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(54) AMIDE DERIVATIVES OR SALTS THEREOF

AMIDDERIVATE ODER DEREN SALZE

DERIVES AMIDES OU SELS DESDITS DERIVES

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JP-A- 9 512 275
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- **PATENT ABSTRACTS OF JAPAN vol. 1998, no. 13, 30 November 1998 (1998-11-30) & JP 10 218861 A (YAMANOUCHI PHARMACEUT CO LTD), 18 August 1998 (1998-08-18)**

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The file contains technical information submitted after the application was filed and not included in this specification

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Description

Technical Field:

[0001] The present invention relates to pharmaceutical amide derivatives or salts thereof and to therapeutic agents for diabetes mellitus containing them as effective components.

Background of the Invention:

[0002] Diabetes mellitus is a disease accompanied by a continuous hyperglycemic state and is said to be caused by action of many environmental and genetic factors. The main controlling factor for blood sugar is insulin, and it has been known that hyperglycemia is caused by deficiency of insulin or by excess of factors which inhibit its action (such as genetic cause, lack of exercise, obesity and stress).

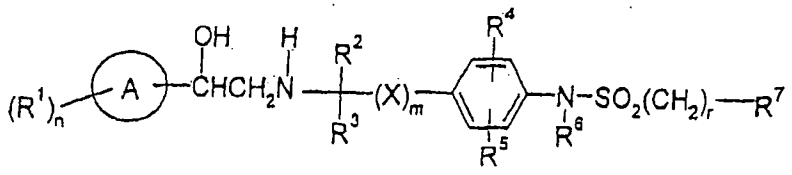
[0003] Diabetes mellitus is classified mainly into insulin-dependent diabetes mellitus (IDDM, caused by lowering of insulin-secreting pancreas function due to autoimmune diseases) and non-insulin-dependent diabetes mellitus (NIDDM, caused by lowering of insulin-secreting pancreas function due to pancreatic fatigue accompanied by continuous high insulin secretion); 95% or more of diabetic patients in Japan are said to suffer from NIDDM, and an increase in patients due to change in daily life style is becoming a problem.

[0004] For therapy of diabetes mellitus, dietetic treatment, therapeutic exercise and treatment of obesity are mainly conducted in mild cases while, when the disease progresses, oral antidiabetic drugs (for example, insulin secretion promoters such as sulfonylurea compounds and insulin sensitivity potentiators) are administered. In severe cases, an insulin preparation is administered. However, there has been a brisk demand for creation of drugs whereby higher control of blood sugar is possible, and development of antidiabetic drugs having a new mechanism and high usefulness has been demanded.

[0005] U.S. Patents 4,396,627 and 4,478,849 describe phenyl-ethanolamine derivatives useful as drugs for obesity and for hyperglycemia. Action of those compounds is reported to be due to a stimulating action to β_3-receptors. It is known that β-adrenaline receptors are classified into β_1, β_2 and β_3 subtypes, that stimulation of β_1-receptor causes increase in heart rate, that stimulation of β_2-receptor stimulates decomposition of glycogen in muscles (whereby synthesis of glycogen is inhibited, causing an action such as muscular tremor),and that stimulation of β_3-receptor shows anti-obesity and anti-hyperglycemia actions (such as decrease in triglyceride and cholesterol and increase in HDL-cholesterol).

[0006] However, those β_3-agonists also have actions caused by stimulation of β_1- and β_2-receptors such as increase in heart rate and muscular tremor, and they have a problem in terms of side effects.

[0007] Recently, it was ascertained that β-receptors differ amongst species, and it has been reported that even compounds confirmed to have a β_3-receptor selectivity in rodential animals such as rats show stimulating action to β_1- and β_2-receptors in human beings. In view of this, investigations for compounds having a stimulating action which is selective to β_3-receptor in humans have been conducted recently using human cells or cells where human receptors are expressed. WO 95/29159 describes substituted sulfonamide derivatives of formula A below which, due to their selective stimulating action to β_3-receptors in human beings, are useful against obesity, hyperglycemia etc. - but does not specifically disclose insulin secretion promoting and insulin sensitivity potentiating actionsof those compounds.



(A)

[0008] In formula A the symbols are as defined in WO95/29159.

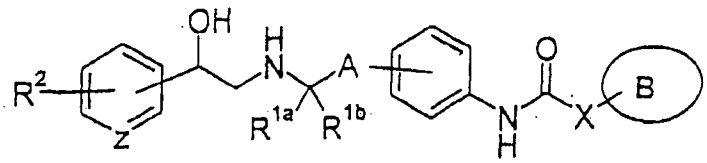
[0009] There has thus been demand for creation of therapeutic agents for diabetes mellitus of a new type which have high clinical usefulness.

Disclosure of the Invention:

[0010] The present inventors have conducted intensive investigation on compounds having both insulin secretion promoting and insulin sensitivity potentiating actions and found novel amide derivatives that show both good insulin

secretion promoting action and good insulin sensitivity potentiating action and furthermore show selective stimulating action to β_3-receptors.

[0011] The present invention provides amide derivatives of formula (I) below, and salts thereof, that are useful for the therapy of diabetes mellitus, having both insulin secretion promoting and insulin sensitivity potentiating actions and further having anti-obesity and anti-hyperlipemia actions due to selective stimulating action to β_3-receptors. It also provides pharmaceutical compositions containing these compounds as effective ingredients, and the use of these compounds for preparation of medicaments for treating diabetes mellitus. In the compounds of formula (I)



(I)

ring B is a heteroaryl group which may be substituted and may be fused and which is as defined below;

X is a bond; lower alkylene or alkenylene which may be substituted with hydroxy or a lower alkyl group; carbonyl; or -NH-; with the proviso that when X is a lower alkylene group which may be substituted with a lower alkyl group, the hydrogen atoms bonded to the carbon atom constituting the ring B may form a lower alkylene group together with the lower alkyl group so that a ring is formed;

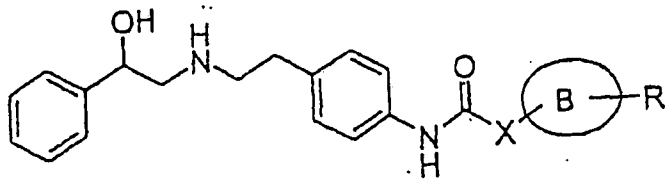
A is methylene, ethylene or $-CH_2-O-$;

R^{1a} and R^{1b} are the same or different and selected from H and lower alkyl groups;

R^2 is H or halogen; and

Z is N or =CH-.

[0012] The optionally fused heteroaryl group ring B is selected from imidazothiazol, thioxothiazol, tetrahydrobenzothiazol, tetrahydroquinolinyl, quinolyl, isoquinolyl, quinazolinyl, quinolidinyl, quinoxalinyl, cinnolinyl, benzimidazolyl, imidazopyridyl, benzoisoxazolyl, benzoxazolyl, benzothiazolyl, oxazolopyridyl, isothiazolopyridyl, pyrrolyl, imidazolyl, thiazolyl, pyrazolyl, isothiazolyl, isoxazolyl, pyridyl, pyrimidyl, pyridazinyl, pyrazinyl, thiadiazolyl, triazolyl, tetrazolyl, naphthyridinyl and pyridopyrimidinyl groups; and the heteroaryl group has its optional substitutent(s) selected from halogens and lower alkyl, lower alkenyl, lower alkynyl, hydroxy, sulfanyl, halogeno lower alkyl, lower alkyl-O-, lower alkyl -S-, lower alkyl-O-CO-, carboxy, sulfonyl, sulfinyl, lower alkyl-SO-, lower alkyl-SO_2-, lower alkyl-CO-, lower alkyl-CO-O-, carbamoyl, lower alkyl-NH-CO-, di-lower alkyl-N-CO-, nitro, cyano, amino, lower alkyl-NH-, di-lower alkyl-N-, benzyl, halogenobenzyl, cyanobenzyl, nitrobenzyl, trifluoromethylbenzyl, isopropylbenzyl, phenylbenzyl, methoxycarbonylbenzyl, piperidinecarbonyl benzyl, benzyloxy, benzylsulfanyl, phenylamino, fluorophenylamino, phenylethyl, phenyl, naphthyl, quinolinyl, pyridylmethyl, guanidino, lower alkyl-CO-NH - and lower alkyl-SO_2-NH-groups. In some compounds according to the invention R^2, R^{1a} and R^{1b} are each H and Z is =CH-, for example as in amide derivatives of formula (Ia) below and salts thereof



(Ia)

where ring B is a heteroaryl group, X is a bond or a lower alkylene group, and R is H or halogen or a lower alkyl, amino, benzyl or halogenobenzyl group.

[0013] The term "lower" herein means a linear or branched hydrocarbon chain having up to 6 carbon atoms unless otherwise specified.

[0014] Specific examples of the "lower alkyl group" are methyl, ethyl, and linear or branched propyl, butyl, pentyl and hexyl, preferably an alkyl having from 1 to 4 carbon atoms, particularly preferably methyl, ethyl, propyl and isopropyl.

[0015] A "lower alkylene group" is a divalent group obtained by removing an arbitrary hydrogen atom from the above "lower alkyl group"; preferred are alkylene groups having from 1 to 4 carbon atoms, particularly methylene, ethylene, propylene and butylene. Examples of the "lower alkenylene group" are vinylene, propenylene, butenylene, pentenylene

and hexenylene groups.

[0016] Specific examples of ring B when it is a heteroaryl group fused with a benzene ring, or is a monocyclic or bicyclic heteroaryl group, are quinolyl, isoquinolyl, quinazolinyl, quinolidinyl, quinoxalinyl, cinnolinyl, benzimidazolyl, imidazopyridyl, benzoisoxazolyl, benzoxazolyl, benzothiazolyl, oxazolopyridyl, isothiazolopyridyl, pyrrolyl, imidazolyl, thiazolyl, pyrazolyl, isothiazolyl, isoxazolyl, pyridyl, pyrimidyl, pyridazinyl, pyrazinyl, thiadiazolyl, triazolyl, tetrazolyl, naphthyridinyl and pyridopyrimidinyl groups.

[0017] Preferred examples of substituent for the heteroaryl group which may be fused with a benzene ring are halogen and lower alkyl, lower alkenyl, lower alkynyl, hydroxy, sulfanyl, halogeno lower alkyl, lower alkyl-O-, lower alkyl-S-, lower alkyl-O-CO-, carboxy, sulfonyl, sulfinyl, lower alkyl-SO-, lower alkyl-SO_2-, lower alkyl-CO-, lower alkyl-CO-O-, carbamoyl, lower alkyl-NH-CO-, di-lower alkyl-N-CO-, nitro, cyano, amino, guanidino, lower alkyl-CO-NH-, lower alkyl-SO_2-NH-, lower alkyl-NH- and di-lower alkyl-N- groups.

[0018] These substituents may further be substituted with an aryl or heteroaryl group, halogen or a hydroxy, sulfanyl, halogeno lower alkyl, lower alkyl-O-, lower alkyl-S-, lower alkyl-O-CO-, carboxy, sulfonyl, sulfinyl, lower alkyl-SO-, lower alkyl-SO_2-, lower alkyl-CO-, lower alkyl-CO-O-, carbamoyl, lower alkyl-NH-CO-, di-lower alkyl-N-CO-, nitro, cyano, amino, guanidino, lower alkyl-CO-NH-, lower alkyl-SO_2-NH-, lower alkyl-NH- or di-lower alkyl-N- group. These substituents such as an aryl or heteroaryl group etc. may further be substituted with halogen etc.

[0019] The "lower alkenyl group" is a linear or branched alkenyl group having 2 to 6 carbon atoms, and specific examples are vinyl, propenyl, butenyl, pentenyl and hexenyl groups.

[0020] The "lower alkynyl group" is a linear or branched alkynyl group having 2 to 6 carbon atoms, and specific examples are ethynyl, propynyl, butynyl, pentynyl and hexynyl.

[0021] The "halogen" means a fluorine, chlorine, bromine or iodine atom, and the "halogeno lower alkyl group" means a group where an arbitrary hydrogen atom or atoms in the above alkyl group is/are substituted with a halogen atom or atoms.

[0022] When X is a bond, the carbon atom of the -CO- group is directly bonded to the ring B.

[0023] Each compound of the present invention has at least one asymmetric carbon atom and therefore there are optical isomers such as (.R) -compounds, (S) -compounds etc., racemates, diastereomers, etc. The present invention includes all and each of the isolated isomers and mixtures thereof. It also includes hydrates, solvates (such as those with ethanol) and polymorphic substances of derivative (I).

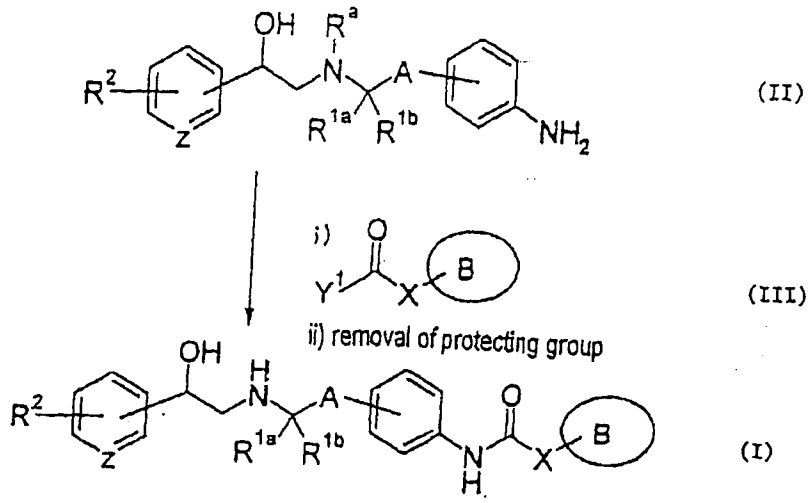
[0024] Derivative (I) of the present invention may form salts with acids - e.g. addition salts with mineral acids such as hydrochloric, hydrobromic, hydroiodic, sulfuric, nitric and phosphoric acids etc. and with organic acids such as formic, acetic, propionic , oxalic, malonic, succinic, fumaric, maleic, lactic, malic, citric, tartaric, carbonic, picric, methanesulfonic, ethanesulfonic and glutamic acids etc.

Manufacturing Method

[0025] The compound of the present invention may be manufactured by . various synthetic methods utilizing the characteristics of its fundamental skeleton and the type of any substituent(s). Representative methods are illustrated hereunder.

First Manufacturing Method:

[0026]



[0027] In the formulae, R^{1a}, R^{1b}, R^2, A, B, X and Z are as defined already; R^a is a protective group for amino; and Y^1 is a leaving group, more specifically hydroxy, lower alkoxy or halide.

[0028] In this method, compounds (II) and (III) are subjected to amidation, and the protective group is then removed to synthesize compound (I).

[0029] The amidation can be conducted in customary manner.

[0030] The solvent may vary depending upon Y^1 of compound (III) and mostly an inert solvent or an alcoholic solvent (such as isopropanol etc.) may be applied.

[0031] When Y^1 is a hydroxy group, the reaction may be conducted in the above solvent in the presence of a condensing agent, examples of which are N,N'-dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI), 1,1'-carbonyldiimidazole (CDI), diphenylphosphoryl azide (DPPA), diethylphosphoryl cyanide (DEPC) etc.

[0032] When Y^1 is lower alkoxy, the reaction may be conducted under heating or reflux as it is or in the above inert solvent.

[0033] When Y^1 is halide, the reaction may be conducted in the above inert solvent in the presence of a base.

[0034] Examples of the inert solvent are dimethylformamide (DMF), dimethylacetamide, tetrachloroethane, dichloromethane, dichloroethane, chloroform, carbon tetrachloride, tetrahydrofuran, dioxane, dimethoxyethane, ethyl acetate, benzene, toluene, xylene, acetonitrile, dimethyl sulfoxide etc., and mixtures thereof, and it may be appropriately selected depending upon reaction conditions. Examples of the base are inorganic bases such as sodium and potassium hydroxide and carbonate etc. and organic bases such as N-methylmorpholine, triethylamine, diisopropylethylamine, pyridine etc.

[0035] The protactive group R^a is one commonly used for amino by those skilled in the art, and representative examples are acyl such as formyl, acetyl, propionyl, methoxyacetyl, methoxypropionyl, benzoyl, thienylacetyl, thiazolylacetyl, tetrazolylacetyl, thiazolylglyoxyloyl, thienylglyoxyloyl etc.; lower alkoxycarbonyl such as methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl etc.; aralkyloxy-carbonyl such as benzyloxycarbonyl, p-nitrobenzyloxycarbonyl etc.; lower alkanesulfonyl such as methanesulfonyl, ethanesulfonyl etc.; aralkyl such as benzyl, p-nitrobenzyl, benzhydryl, trityl, etc.; tri-(lower alkyl)silyl such as trimethylsilyl etc.; and the like.

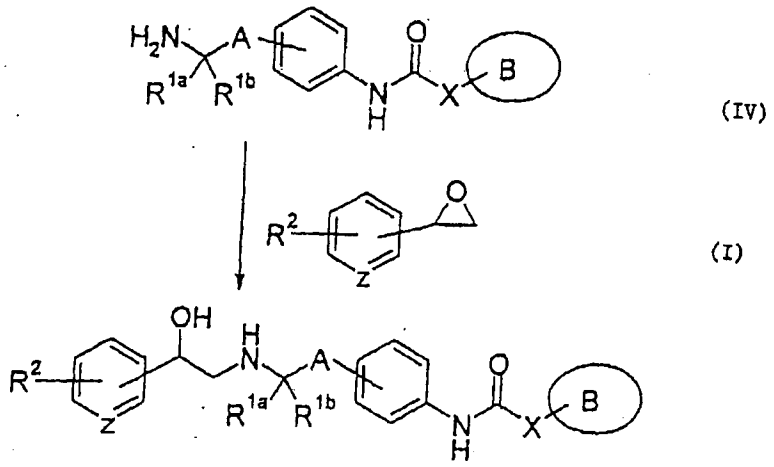
[0036] Removal of the protective group may be conducted in customary manner. For example, R^a may be easily removed

i) when it is benzhydryl, p-methoxybenzyl, trityl, tert-butoxycarbonyl, formyl etc., by treatment with an acid such

as formic or trifluoroacetic acid or a trifluoroacetic acid-anisole, hydrobromic acid-acetic acid or hydrochloric acid-dioxane mixed solution etc;
ii) when it is benzyl, p-nitrobenzyl, benzhydryl, trityl etc.,by catalytic reduction using palladium-carbon or palladium hydroxide-carbon; and iii) when it is tri-(lower alkyl)silyl or the like, by treatment with water, fluoride anion (e.g. tetra-n-butylammonium fluoride, sodium fluoride, potassium fluoride, hydrofluoric acid) etc.

Second Manufacturing Method:

[0037]



[0038] In the formulae, R^{1a}, R^{1b}, R^2, A, B, X and Z are as defined already.

[0039] In this method, compound (IV) is reacted with compound (V) to give compound (I).

[0040] Compounds (IV) and (V) are reacted under heating or reflux for 1 to 24 hours, as they are or in an inert solvent, to give compound (I).

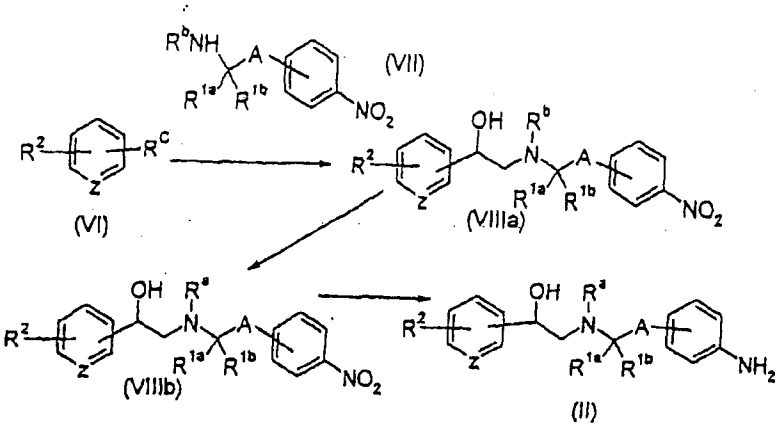
[0041] Examples of the inert solvent are acetonitrile, tetrahydrofuran, 2-butanone, dimethyl sulfoxide and N-methylpyrrolidone. A base such as sodium or potassium carbonate or diisopropylethylamine may be added to the reaction mixture.

[0042] In the above methods, it is possible to purify the resulting substance by removing undesired by-products by recrystallization, pulverization, preparative thin layer chromatography, silica gel flash chromatography (as described in W. C. Still, et al. , *J. Org. Chem.*, **43**, 2923 (1978)), medium-pressure liquid chromatography and HPLC. The compound produced through HPLC can be isolated as a corresponding salt.

[0043] The starting material used in the above-mentioned methods may be easily manufactured by methods which are known to those skilled in the art - e.g. as shown hereunder.

Manufacturing Method for Starting Compound (II)

[0044]



[0045] In the formulae, R^{1a}, R^{1b}, R^2, R^a, A and Z have are as defined already; R^b is H or an aralkyl-based protective group for amino; and R^c is epoxy, 2-haloacetyl or 1-carboxymethan-1-ol.

[0046] This method is composed of step (a) in which compound (VI) is reacted with compound (VII), followed by reduction to give compound (VIIIa) depending upon the type of R^c ; step (b) where protection is conducted when R^b of compound (VIIIa) is H; and step (c) where nitro is reduced to amino to give compound (II).

[0047] Examples of the aralkyl-based protective group for amino Ln this method are benzyl, p-nitrobenzyl, benzhydryl etc.

Step (a):

[0048] Illustration is made for the following three cases:

1) When R^c is epoxy, compound (VI) may be reacted with compound (VII) as in the second manufacturing method. Reaction conditions such as reaction temperature, solvent etc. are also the same.

2) When R^c is 2-haloacetyl, compound (VI) is reacted with compound (VII) in the presence of a base, followed by reduction to compound (VIIIa). The base is the same as in the first manufacturing method. The reduction may be conducted in the above inert solvent or in a solvent of an alcohol type with stirring in the presence of a reducing agent. Examples of the reducing agent are sodium borohydride or cyanoborohydride, lithium aluminum hydride, borane etc.

3) When R^c is 1-carboxymethan-1-ol, compound (VI) is reacted with compound (VII) in the presence of a condensing agent, followed by reduction as in 2) to compound (VIIIa). The condensing agent is the same as in the first manufacturing method.

Step (b):

[0049] When R^b in compound (VIIIa) is H, the amino group is protected in customary manner using di-tert-butyl dicarbonate etc., to prepare compound (VIIIa).

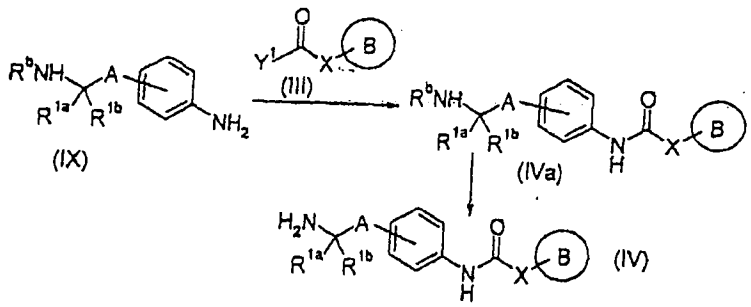
Step (c) :

[0050] The reduction of nitro to amino may be conducted in customary manner such as metallic reduction using iron, zinc etc. and catalytic reduction using a catalyst such as palladium-carbon, palladium hydroxide-carbon, Raney nickel etc. R^a becomes H depending upon the reduction conditions, but it may be protected again in customary manner.

Manufacturing Method for Starting Compound (IV)

[0051]

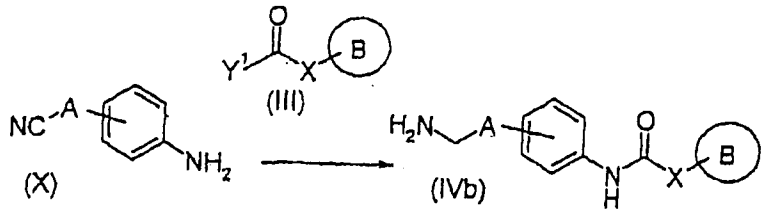
A)



[0052] In the formulae, R^{1a}, R^{1b}, R^b, A, B, X and Y^1 are as defined already.

[0053] This is a reaction where . compounds (IX) and (III) are subjected to amidation to give compound (IVa), and when R^b is a protective group for amino it is removed to give compound (IV). The amidation reaction can be conducted as in the first manufacturing method, and the reaction conditions such as reaction temperature, solvent etc. are also the same.

B)



[0054] This is a reaction where compounds (X) and (III) are subjected to amidation and then to reduction to give compound (IVb). The amidation can be conducted as in the first manufacturing method, and the reaction conditions such as reaction temperature, solvent are also the same. In the reduction, the above catalytic reduction, or a method where reduction is conducted using sodium borohydride in the presence of cobalt chloride, may be applied.

[0055] For other starting compounds - such as (III), (V), (VI) and (VII) - those which are available in the market or are appropriately synthesized by known methods (such as N-alkylation, cyclization, hydrolysis etc.) from the commercially available compounds may be used.

[0056] The derivative of the present invention which is manufactured as such is isolated and purified as a free compound, a salt thereof obtained by means of salt formation in customary manner, a hydrate, a solvate with various solvents such as ethanol etc., or polymorphic crystals etc. The isolation and purification may be conducted by common chemical operations such as extraction, concentration, evaporation, crystallization, filtration, recrystallization, various chromatographic methods etc.

[0057] Various isomers may be isolated in customary manner utilizing their physico-chemical differences.

[0058] For example, the racemate can be converted to stereochemically pure isomers by common racemic resolution - such as changing it to diastereomer salts with usual optically active (for example tartaric) acid followed by optical resolution, and the like.

[0059] A mixture of diastereomers may be separated by customary methods such as fractional crystallizaiton or chromatography etc. An optically active compound be manufactured starting from an appropriate optically active material.

Industrial Applicability:

[0060] The derivatives(I) and salts thereof have both insulin secretion promoting and insulin sensitivity potentiating actions and also selective β_3-receptor stimulating action, and so are useful as therapeutic agents for diabetes mellitus.

[0061] As confirmed below by glucose tolerance and hypoglycemic tests in insulin-resisting model animals, the compounds of the present invention have both good insulin secretion promoting and good insulin sensitivity potentiating actions, so that their usefulness in diabetes mellitus is expected. Although the β_3-receptor stimulating action may participate in expression of the insulin secretion promoting and insulin sensitivity potentiating actions, other mechanism might also participate therein, and the details thereof are still unknown. The β_3-receptor stimulating action of the compounds of the present invention is selective to β_3-receptors in human being. It is known that the stimulation of β_3-receptor stimulates decomposition of fat (of fat tissue triglyceride into glycerol and free fatty acid), whereby disappearance of fat mass is promoted. Therefore the compounds of the present invention have anti-obesity and anti-hyperlipemia actions (such as triglyceride lowering, cholesterol lowering, and HDL cholesterol increasing action) and are useful as preventive and therapeutic agents for obesity and hyperlipemia (such as hypertriglyceridemia, hypercholesterolemia and hypo-HDL-lipoproteinemia). These diseases are known as animus factors in diabetes mellitus, and their amelioration is also useful for prevention and therapy of diabetes mellitus.

[0062] The compound of the present invention is also useful as a preventive and therapeutic agent for other diseases where improvement of symptom can be achieved by reducing the symptoms of obesity and hyperlipemia - i.e. ischemic coronary diseases such as arteriosclerosis, myocardial infarction, angina pectoris etc; cerebral arteriosclerosis such as cerebral infarction etc; or aneurysm etc.

[0063] Further, the selective β_3-receptor stimulating action of the compound of the present invention is useful for prevention and therapy of several diseases reported to be improved by β_3-receptor stimulation. Examples of these are as follows.

[0064] It has been mentioned that the β_3-receptor mediates the motility of non-sphincteral smooth muscle contraction, and because it is believed that selective β_3-receptor stimulating action assists pharmacological control of intestinal motility without accompanying cardiovascular action, the compound of the present invention may be useful in therapy of diseases caused by abnormal intestinal motility such as various gastrointestinal diseases including irritable colon syndrome. It is also useful as a therapy for peptic ulcer, esophagitis, gastritis and duodenitis (including that induced by H. pylori), and enterelcosis (such as inflammatory intestinal diseases, ulcerative colitis, clonal disease and proctitis).

[0065] The β_3-receptor affects the inhibition of release of neuropeptide of some sensory fibers in lungs. The sensory nerve plays an important role in neurogenic inflammation of the respiratory tract (including cough) and so the specific β_3-agonist of the present invention is useful in the therapy of neurogenic inflammation and in addition has little action on the cardiopulmonary system.

[0066] Moreover, the β_3-adrenaline receptor is capable of causing selective antidepressant action due to stimulation of the β_3-receptor in the brain, and so the compound of the present invention may be useful as an antidepressant.

[0067] The action of the compound of the present invention has been ascertained, by experiments using cells expressing human type receptors, to be selective to β_3-receptors, adverse action as caused by other β_3-receptor stimulation being low or none.

[0068] Effects of the compound of the present invention have been ascertained by the following tests.

1. Hypoglycemic test in kk mice (insulin-resisting model; obesity and hyperglycemia):

Male kk mice (blood sugar level: not lower than 200 mg/dl) were subjected to measurement of blood sugar level under feeding and then randomly classified into groups. The drug to be tested was compulsorily administered orally or subcutaneously once daily for four days, and the blood sugar level after 15 to 18 hours from the final administration was compared with that before the administration (n = 6). The blood was collected from a tail vein of the mice using a glass capillary (previously treated with heparin), the protein was removed therefrom, and the amount of glucose in the supernatant liquid (mg/dl) was measured colorimetrically by a glucose oxidase method. The dose at which the blood sugar level was lowered by 30% compared to that before administration of the test drug was expressed as an ED_{30} value.

The compound of the present invention significantly lowered blood sugar level compared to that before its administration - whether oral or subcutaneous.

Some compounds of the present invention exhibited strong activity so that the ED_{30} value for oral administration was 3 mg/kg/day or less.

In WO 95/29159, the compound of Example 90 had an ED_{30} value of 30 mg/kg/day or more, and that of Example 92 an ED_{30} value of 30 mg/kg/day. From this it is clear that the compounds of the present invention have greater potentiating action to insulin sensitivity than those of WO 95/29159.

2. Glucose tolerance test in normal rats:

Male rats of SD strain, seven weeks old, were fasted for a whole day and night, then randomly classified into groups and subjected to an oral glucose tolerance test (OGTT) (n = 4). The compound to be tested was administered orally or subcutaneously 30 minutes before administration of glucose (2 g/kg, po). The blood was collected from the abdominal aorta of the rats anesthetized with pentobarbital (65 mg/kg) - using a heparin-treated glass syringe, the protein was removed therefrom, and the amount of glucose in the supernatant liquid (mg/dl) was measured colorimetrically by a glucose oxidase method. The insulin value in blood was determined by measuring the amount of insulin in plasma (ng/ml) by radioimmunoassay (RIA).

In a group where the compound of the present invention was administered orally or subcutaneously, a significant increase in the insulin value in blood was observed compared to the group to which no drug was given. Increase in sugar blood level after administration of glucose was significantly inhibited as well. From this it is apparent that the compound of the present invention has good insulin secretion promoting and hyperglycemia inhibiting actions.

3. Stimulating test to human β_3-, β_2- and β_1-receptors:

Human β_3-stimulating action was investigated using an SK-N-MC cell system (cells in which human β_3-receptor and human β_1-receptor were permanently expressed were purchased) while human β_2- and β_1-stimulating actions were investigated using a CHO cell system (cells in which each of human β_2- and β_1-receptors was compulsorily expressed were purchased). Stimulating action of the compound (10^{-10} to 10^{-4} M) was investigated by incubating 10^5 cells/well of each of the cells on a 24-well plate and checking under a subconfluent state after two days using the producing activity of cyclic AMP (cAMP) as an index. The human β_3-stimulating action was investigated in the presence of a β_1-receptor blocker (CGP20712A, 10^{-6}M). Amount of production of cAMP in each cell (pmol/ml) was measured by an RIA method using ^{125}I-cAMP. Intensity of action of each compound was compared by calculating the pD2 value and the maximum activity (I.A. (%) where the maximum reaction of 10^{-6} M isoproterenol was defined as 100%) from the resulting dose-reaction curve.

[0069] As a result, it has been ascertained that the compound of the present invention has a selective stimulating action to human β_3-receptor.

[0070] A pharmaceutical composition containing one or more compounds of the present invention as an effective ingredient is prepared using common pharmaceutically acceptable vehicles. Administration may be oral, or parenteral - by, for example, injection, suppository, subcutaneous agent, inhaling agent or intracystic infusion.

[0071] The dose may be appropriately decided in each particular case taking into consideration symptom, age, sex etc. of the patient - but usually is around 0.01 to 100 mg/kg per day for adults for oral administration, as a single dose or divided into 2 to 4 times a day. When intravenous injection is conducted, depending upon the symptom, the dose is usually around 0.001 to 10 mg/kg per day for adults, administered as a single dose or divided into two or more times a day.

[0072] As a vehicle for the preparation, nontoxic solid or liquid substances for pharmaceuticals may be used.

[0073] Examples of solid composition for oral administration are tablets, pills, capsules, diluted powder and granules. In such a solid composition, one or more active substances are mixed with at least one inert excipient such as lactose, mannitol, glucose, hydroxypropyl cellulose, microcrystalline cellulose, starch, polyvinylpyrrolidone, agar, pectin, magnesium metasilicate aluminate and magnesium aluminate. The composition may also contain additives other than inert excipient (e.g. lubricants such as magnesium stearate, disintegrants such as calcium cellulose glycolate, stabilizers such as lactose, and auxiliary solubilizers such as glutamic or aspartic acid) in customary manner. Tablets and pills may, if necessary, be coated with sugar such as sucrose, gelatin, hydroxypropyl cellulose, hydroxypropylmethyl cellulose phthalate etc., or with film of gastric or enteric coating substances.

[0074] The liquid composition for oral administration includes pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs and contains commonly used inert excipients such as purified water or ethanol. It may further contain auxiliary agents such as moisturizing or suspending agents, sweeteners, taste agents, aromatic agents and antiseptic agents. The injection for parenteral administration includes aseptic aqueous or non-aqueous solutions, suspensions and emulsions. The non-aqueous solutions and suspensions include, for example, distilled water for injection and physiological saline solution. Examples of the solvent for non-aqueous solution and suspension are propylene glycol; polyethylene glycol; plant oils such as cacao butter, olive oil and sesame oil; alcohols such as ethanol;

gum arabic; and Polysolvate 80 (trade name). Such a composition may further contain auxiliary agents such as isotonizing agents; antiseptic agents; moisturizing agents; emulsifiers; dispersing agents; stabilizers such as lactose; and auxiliary solubilizers such as glutamic and aspartic acids. The liquid composition may be sterilized, for example, by filtration through a bacteria-preserving filter or by irradiation or compounding with a bactericide; it may also be made by manufacturing a sterile solid composition, followed by dissolving in sterile water or a sterile solvent for injection before use.

Best Mode for Carrying Out the Invention:

[0075] The present invention is further illustrated by way of Examples hereunder. The present invention is not limited to compounds mentioned in the Examples but covers all derivatives of formula (I), salts thereof, hydrates thereof, geometric and optical isomers thereof and polymorphic forms thereof. Novel starting materials used in the Examples are illustrated by the following Referential Examples.

Referential Example 1:

[0076] To a mixed solution of ethyl acetate and a 1N aqueous solution of sodium hydroxide was added 25.2 g of 4-nitrophenyl ethylamine hydrochloride, and the mixture was vigorously stirred. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated. To the resulting residue were added 100 ml of 2-propanol and 15.0 g of (R)-styrene oxide successively, and the reaction mixture was heated to reflux for 12 hours. The solvent was evaporated in vacuo, and the residue was purified by silica gel column chromatography (eluent: chloroform/methanol = 100/1 → 10/1). The resulting residue was again subjected to silica gel column chromatography (eluent: hexane/ethyl acetate/triethylamine = 1/5/trace) to give 8.05 g of (R)-1-phenyl-2-[[2-(4-nitrophenyl)ethyl]amino]ethanol.

Referential Example 2:

[0077] A solution of 8.02 g of (R)-1-phenyl-2-[[2-(4-nitrophenyl)ethyl]amino]ethanol and 6.30 g of di-tert-butyl dicarbonate in 80 ml of tetrahydrofuran was stirred for 12 hours at room temperature. The residue obtained by evaporation of the solvent was purified by silica gel column chromatography (eluent: hexane/ethyl acetate = 3/1) to give 10.8 g of tert-butyl (R)-N-(2-hydroxy-2-phenylethyl)-N-[2-(4-nitrophenyl)ethyl]carbamate.

Referential Example 3:

[0078] To a solution of tert-butyl (R)-N-(2-hydroxy-2-phenylethyl)-N-[2-(4-nitrophenyl)ethyl]carbamate in 200 ml of ethanol was added 1.03 g of 10% palladium-carbon and the mixture was stirred for two hours at room temperature in a hydrogen atmosphere under atmospheric pressure. Insoluble matters were removed using Celite, and the filtrate was concentrated in vacuo to give 9.54 g of tert-butyl (R)-N-[2-(4-aminophenyl)-N-(2-hydroxy-2-phenylethyl)ethyl]-carbamate.

Referential Example 4:

[0079] To a solution of 448 mg of tert-butyl (R)-N-[2-(4-aminophenyl)-N-(2-hydroxy-2-phenylethyl)ethyl]carbamate and 330 mg of triethylamine in 4 ml of chloroform was added 146 mg of 2-pyridinecarbonyl chloride. The reaction solution was stirred at room temperature for two hours, and the solvent was evaporated in vacuo. The residue was diluted with chloroform, and the organic layer was washed with a saturated aqueous solution of sodium hydrogen carbonate and dried over anhydrous magnesium sulfate. The residue obtained by evaporating the solvent in vacuo was purified by silica gel column chromatography (eluent: hexane/ethyl acetate = 1/3) to give 321 mg of tert-butyl (R)-N-(2-hydroxy-2-phenylethyl)-N-[2-[4-[(2-pyridinecarbonyl)amino]phenyl]ethyl]carbamate.

Referential Example 5:

[0080] To a solution of 377 mg of tert-butyl (R)-N-[2-(4-aminophenyl)-N-(2-hydroxy-2-phenylethyl)ethyl]carbamate in 10 ml of tetrahydrofuran were added 203 mg of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, 143 mg of 1-hydroxybenzotriazole and 202 mg of 8-quinolinecarboxylic acid successively. The reaction solution was stirred at room temperature for 18.5 hours, and the solvent was evaporated in vacuo. The residue was diluted with ethyl acetate, and the organic layer was washed with a saturated aqueous solution of sodium hydrogen carbonate and dried over anhydrous magnesium sulfate. The residue obtained by evaporation of the solvent was purified by silica gel column chromatography (eluent: hexane/ethyl acetate = 2/1) to give 302 mg of tert-butyl (R)-N-(2-hydroxy-2-phenylethyl)

-N-[2-[4-[(8-quinolinecarbonyl)amino]phenyl]ethyl]carbamate.

Referential Example 6:

[0081] To a solution of 403 mg of tert-butyl (R)-N-(2-hydroxy-2-phenylethyl)-N-[2-[4-[(2-1H-imidazol-2-ylacetyl)amino]phenyl]ethyl]carbamate in 10 ml of acetonitrile were added 120 mg of potassium carbonate and 164 mg of 2-fluorobenzyl bromide successively at room temperature. The reaction solution was stirred at 50°C for 12 hours. Insoluble matters were filtered off using Celite, and the solvent was evaporated. The resulting residue was purified by silica gel column chromatography to give 253 mg of tert-butyl (R)-N-[2-[4-[[2-[1-(2-fluorobenzyl)-1H-imidazol-2-yl]acetyl]amino] phenyl]ethyl]-N-(2-hydroxy-2-phenylethyl)-carbamate.

Referential Example 7:

[0082] To a solution of 13.4 g of (R)-2-[N-benzyl-N-[2-(4-nitrophenyl)ethyl]amino]-1-phenylethanol in 150 ml of methanol were added 8.6 g of iron powder and 40 ml of a 2N aqueous hydrochloric acid solution. The reaction mixture was heated to reflux for two hours, a 1N aqueous solution of sodium hydroxide was added thereto, and the insoluble matters thus produced were filtered off using Celite. The filtrate was concentrated in vacuo to remove the methanol. The resulting aqueous phase was extracted with chloroform, the organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated in vacuo. The resulting residue was purified by silica gel column chromatography (eluent: hexane/ethyl acetate = 1/1) to give 11.45 g of (R)-2-[N-[2-(4-aminophenyl)ethyl]-N-benzylamino]-1-phenylethanol.

Referential Example 8:

[0083] To 502 mg of (R)-2-[N-[2-(4-aminophenyl)ethyl]-N-benzylamino]-1-phenylethanol were added 336 mg of ethyl 2-(3-methylpyridin-2-yl)acetate and 10 ml of xylene. The reaction mixture was refluxed for nine hours, and the solvent was evaporated in vacuo. The resulting residue was purified by silica gel column chromatography (eluent: hexane/ethyl acetate = 1/3) to give 222 mg of (R)-4'-[2-[N-benzyl-N-(2-hydroxy-2-phenylethyl)amino]ethyl]-2-(3-methylpyridin-2-yl)acetanilide.

Referential Example 9:

[0084] To a solution of 0.96 g of 2-fluoroacetophenone in 20 ml of tetrahydrofuran was added 2.65 g of benzyltrimethylammonium tribromide. The reaction mixture was stirred at room temperature for 30 minutes, insoluble matters were filtered off, and the solvent was concentrated in vacuo. The resulting residue was dissolved in 40 ml of 2-butanone, then 1.81 g of N-benzyl-4-nitrophenethylamine and 0.92 g of diisopropyl ethylamine were added, and the reaction mixture was heated to reflux for one hour. The solvent was evaporated in vacuo, ethyl acetate was added thereto, and the mixture was washed with water and a saturated saline solution successively. The organic layer was dried over anhydrous magnesium sulfate and evaporated in vacuo. The resulting residue was dissolved in 40 ml of methanol, 0.34 g of sodium borohydride was added thereto, and the reaction mixture was stirred at room temperature for one hour. The solvent was evaporated in vacuo, ethyl acetate was added, and the mixture was washed with water and a saturated saline solution successively. The organic layer was dried over anhydrous magnesium sulfate and evaporated in vacuo. The resulting residue was purified by silica gel column chromatography (eluent: chloroform) to give 1.95 g of 2-[N-benzyl-N-[2-(4-nitrophenyl)ethyl]amino]-1-(2-fluorophenyl)ethanol.

Referential Example 10:

[0085] A reaction mixture of 5.12 g of methyl 2-pyridylacetate, 5.14 g of 4-aminobenzyl cyanide and 50 ml of xylene was heated to reflux for 24 hours. An appropriate amount of the solvent was evaporated, diethyl ether was added to the residue, and the resulting crystals were taken by filtration to give 5.65 g of 4'-cyanomethyl-2-(2-pyridyl)acetanilide.

Referential Example 11:

[0086] To a solution of 640 mg of 4'-cyanomethyl-2-(4,6-dimethyl-2-pyridyl)acetanilide in 15 ml of tetrahydrofuran was added 15 ml of an ethanolic suspension of a Raney nickel, and concentrated aqueous ammonia was added to adjust the pH of the mixture to about 10. The mixture was stirred at room temperature for one hour in a hydrogen atmosphere under atmospheric pressure. The reaction mixture was filtered using Celite, and the solvent was evaporated in vacuo to give 640 mg of 4'-(2-aminomethyl)-2-(4,6-dimethyl-2-pyridyl)acetanilide.

Referential Example 12:

[0087] To a solution of 630 mg of 4'-(2-aminomethyl)-2-(4,6-dimethyl-2-pyridyl) acetanilide in 20 ml of toluene was added 0.27 ml of benzaldehyde, and the mixture was heated to reflux for three hours using a Dean-Starke apparatus. The reaction mixture was filtered, and the solvent was evaporated in vacuo. A solution of the resulting residue in 30 ml of methanol was cooled at 0°C, 63 mg of sodium borohydride was added, and the mixture was stirred at 0°C for one hour. About one-half of the solvent of the reaction mixture was evaporated in vacuo, water and ethyl acetate were added to the residue, the organic layer was washed with a saturated saline solution twice and dried over anhydrous magnesium sulfate and the solvent was evaporated in vacuo. To a solution of the resulting residue in 50 ml of isopropanol was added 0.26 ml of (R)-styrene oxide, and the mixture was heated to reflux for 12 hours. The solvent was evaporated in vacuo, and the resulting residue was purified by silica gel column chromatography (eluent: chloroform/methanol = 100/3) to give 920 mg of (R)-4'-[2-[N-benzyl-N-(2-hydroxy-2-phenylethyl)-amino]ethyl]-2-(4,6-dimethyl-2-pyridyl)acetanilide.

Example 1:

[0088] A 4N hydrogen chloride-ethyl acetate solution (10 ml) was added to 10 ml of an ethanolic solution of 458 mg of tert-butyl (R)-N-(2-hydroxy-2-phenylethyl)-N-[2-[4-[(2-pyridinecarbonyl)amino]phenyl]ethyl]carbamate. The reaction solution was stirred at room temperature for three hours, and the solvent was then evaporated in vacuo. The obtained crude crystals were recrystallized from methanol-ethanol-ethyl acetate to give 289 mg of (R)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]-2-pyridinecarboxanilide dihydrochloride.

[0089] The compounds of Examples 2 to 33 were prepared in the same manner as in Example 1.

Example 2:

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-3-pyridinecarboxanilide dihydrochloride

Example 3:

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-8-quinolinecarboxanilide dihydrochloride

Example 4:

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-(E)-3-(2-pyridyl)acrylic anilide dihydrochloride

Example 5:

(R)-2-(Benzothiazol-2-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

Example 6:

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-(imidazo[2,1-b]thiazol-3-yl)acetanilide dihydrochloride

Example 7:

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-(2-methylthiazol-4-yl)acetanilide hydrochloride

Example 8:

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-(1H-imidazol-2-yl)acetanilide dihydrochloride

Example 9:

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-(1H-tetrazol-5-yl)acetanilide hydrochloride

Example 10:

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-(5-sulfanyl-1H-1,2,4-triazol-3-yl)acetanilide hydrochloride

Example 11:

(R)-2-(2-Aminothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]-2-oxoacetanilide dihydrochloride

Example 12:

(R)-2-(5-Amino-1,2,4-thiadiazol-3-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

Example 13:

(R)-2-(5-Ethoxycarbonylamino-1,2,4-thiadiazol-3-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide hydrochloride

Example 14:

(R)-2-[(2-(3-Fluorophenylamino)thiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

Example 15:

(R)-2-(2-Chloropyridin-6-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide hydrochloride

Example 16:

(R)-2-(2-Benzyloxypyridin-6-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide hydrochloride

Example 17:

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-[1-(2-methyl-3-propenyl)-1H-imidazol-2-yl)acetanilide dihydrochloride

Example 18:

(R)-2-(1-Benzyl-1H-imidazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

Example 19:

(R)-2-[1-(2-Chlorobenzyl)-1H-imidazol-4-yl]-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

Example 20:

(R)-2-[1-(3-Chlorobenzyl)-1H-imidazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

Example 21:

(R)-2-[1-(4-Chlorobenzyl)-1H-imidazol-4-yl]-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

Example 22:

(R)-2-[1-(4-Fluorobenzyl)-1H-imidazol-2-yl]-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

Example 23:

(R)-2-[1-(4-Chlorobenzyl)-1H-imidazol-2-yl]-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

Example 24:

(R)-2-[1-(4-Bromobenzyl)-1H-imidazol-2-yl]-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

Example 25:

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-[1-(4-iodobenzyl)-1H-imidazol-2-yl]acetanilide dihydrochloride

Example 26:

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-[1-(4-trifluoromethylbenzyl)-1H-imidazol-2-yl]acetanilide dihydrochloride

Example 27:

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-[1-(2-naphthyl)-1H-imidazol-2-yl]acetanilide dihydrochloride

Example 28:

(R)-2-[1-(4-Fluorobenzyl)-5-methyl-1H-imidazol-2-yl]-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

Example 29:

(R)-2-[1-(4-Fluorobenzyl)-4-methyl-1H-imidazol-2-yl]-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

Example 30:

(R)-2-[1-(4-Fluorobenzyl)-1H-tetrazol-5-yl]-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide hydrochloride

Example 31:

(R)-2-[2-(3,4-Dichlorobenzyl)-1H-tetrazol-5-yl]-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide hydrochloride

Example 32:

(R)-2-[2-(4-Fluorobenzyl)-1H-tetrazol-5-yl]-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide hydrochloride

Example 33:

(R)-2-[1-(3,4-Dichlorobenzyl)-1H-tetrazol-5-yl]-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide hydrochloride

Example 34:

To a solution of 175 mg of tert-butyl (R)-N-[2-[4-[2-(1H-1,2,4-triazol-3-yl)acetylamino]phenyl]ethyl]-N-(2-hydroxy-2-phenylethyl)carbamate in 5 ml of methanol was added 4 ml of a solution of 4N hydrogen chloride in ethyl acetate. The mixture was stirred at room temperature for three hours, the solvent was filtered off, and the resulting powder was washed with ethanol. The resulting powder was dried to give 125 mg of (R)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]-2-(1H-1,2,4-triazol-3-yl)acetanilide dihydrochloride.

[0090] The compounds of Examples 35 to 40 were prepared in the same manner as in Example 34.

Example 35:

(R)-2-(5-Benzylsulfanyl-1H-1,2,4-triazol-3-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

Example 36:

(R)-2-(2-Acetamidothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide hydrochloride

Example 37:

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-(2-methanesulfonamidothiazol-4-yl)acetanilide hydrochloride

Example 38:

(R)-2-(2-Guanidinothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

Example 39:

[0091] (R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-(2-phenylaminothiazol-4-yl)acetanilide hydrochloride

Example 40:

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-[1-(4-nitrobenzyl)-1H-imidazol-2-yl]acetanilide hydrochloride

Example 41:

[0092] To 690 mg of tert-butyl (R)-N-[2-[4-[2-(2-amino-thiazol-4-yl)acetamino]phenyl]ethyl]-N-[(2-hydroxy-2-phenyl)ethyl]carbamate were added 30 ml of methanol and 15 ml of a solution of 4N hydrogen chloride in ethyl acetate, and the mixture was stirred at room temperature for two hours. The solvent was evaporated in vacuo, and the residue was purified by reverse phase column chromatography (eluent: water/methanol = 2/1) to give 310 mg of (R)-2-(2-aminothiazol-4-yl)-4'-[2-(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride.

[0093] The compounds of Examples 42 to 57 were prepared in the same manner as in Example 41.

Example 42:

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-(2-amino-thiazol-4-yl)carboxanilide hydrochloride

Example 43:

(R)-2-(2-Amino-5-methylthiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

Example 44:

(R)-2-(2-Aminothiazol-4-yl)-2-methyl-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]propionanilide hydrochloride

Example 45:

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-(2-amino-4,5,6,7-tetrahydrobenzothiazol-4-yl)carboxanilide dihydrochloride

Example 46:

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-(imidazo[2,1-b]thiazol-6-yl)acetanilide hydrochloride

Example 47:

(R)-2-(1-Benzyl-1H-1,2,4-triazol-5-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide hydrochloride

Example 48:

(R)-2-(1-Benzyl-1H-1,2,4-triazol-3-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide hydrochloride

Example 49:

(R)-2-(3-Benzyl-2-thioxothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide hydrochloride

Example 50:

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-(5,6,7,8-tetrahydroquinolin-8-yl)carboxanilide dihydrochloride

Example 51:

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-(1-phenyl-1H-imidazol-2-yl)acetanilide dihydrochloride

Example 52:

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-[(1-(4-isopropylbenzyl)-1H-imidazol-2-yl)acetanilide dihydrochloride

Example 53:

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-[(1-(4-phenylbenzyl)-1H-imidazol-2-yl)acetanilide dihydrochloride

Example 54:

(R)-2-[1-(2-Chlorobenzyl)-1H-imidazol-2-yl]-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

Example 55:

(R)-2-[1-(3-Chlorobenzyl)-1H-imidazol-2-yl]-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

Example 56:

(R)-2-[1-(3,4-Dichlorobenzyl)-1H-imidazol-2-yl]-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

Example 57:

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-[(1-(2-pyridyl)methyl-1H-imidazol-2-yl)acetanilide dihydrochloride

[0094] The compound of Example 58 was prepared by the same manner as in Example 1.

Example 58:

(R)-2-(2-aminopyridin-6-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

Example 59:

[0095] To a solution of tert-butyl (R)-N-[2-[4-[[2-(2-amino-thiazol-4-yl)-2-oxoacetyl]amino]phenyl]ethyl]-N-(2-hydroxy-2-phenylethyl) carbamate in 30 ml of methanol was added 130 mg of sodium borohydride at room temperature. The reaction mixture was stirred at room temperature for three hours, and the solvent was evaporated in vacuo. The residue was dissolved in 5 ml of methanol, and to this reaction solution was added 10 ml of a solution of 4N hydrogen chloride-ethyl acetate. The reaction solution was stirred at room temperature for eight hours and the solvent was evaporated in vacuo. The residue was purified by silica gel column chromatography (eluent: chloroform/methanol = 5/1). The resulting residue was purified by reverse phase column chromatography (eluent: water/methanol = 2/1) to give 77 mg of (R)-2-(2-amino-thiazol-4-yl)-2-hydroxy-4'-[2-(2-hydroxy-2-phenylethyl)amino]acetanilide hydrochloride.

Example 60:

[0096] To 349 mg of tert-butyl (R)-N-[2-[4-[[2-(2-benzyloxypyridin-6-yl)acetyl]amino]phenyl]ethyl]-N-(2-hydroxy-2-phenylethyl)carbamate were added 478 mg of pentamethylbenzene and 5 ml of trifluoroacetic acid successively. The reaction solution was stirred at room temperature for four hours, and the solvent was evaporated in vacuo. To the residue were added water and potassium carbonate to make the solution basic, and the aqueous phase was extracted with a mixed solvent of chloroform and tetrahydrofuran. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated in vacuo. The residue was purified by silica gel column chromatography (eluent: chloroform/methanol = 10/1 → 5/1). To an ethanolic solution of the resulting residue was added 100 μl of a 4N hydrogen chloride-ethyl acetate solution, and then the solvent was evaporated in vacuo. The resulting crude crystals were recrystallized from ethanol-ethyl acetate to give 65 mg of (R)-2-(2-benzyloxypyridin-6-yl)-4'-[2-[(2-hydroxy-2-phenylethyl) amino]ethyl]acetanilide hydrochloride.

[0097] The compounds of Examples 61 to 76, 83 and 85 were prepared in the same manner as in Example 1; and the compounds of Examples 77 to 82 were prepared in the same manner as in Example 41.

Example 61:

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-(2-methylpropyl-1H-imidazol-2-yl)acetanilide dihydrochloride

Example 62:

(R)-2-[1-(2-Fluorobenzyl)-1H-imidazol-2-yl]-4'-[2-(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

Example 63:

(R)-2-[1-(3-Fluorobenzyl)-1H-imidazol-2-yl]-4'-[2-(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

Example 64:

(R)-2-[1-(2,4-Difluorobenzyl)-1H-imidazol-2-yl]-4'-[2-(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

Example 65:

(R)-2-[1-(2,6-Difluorobenzyl)-1H-imidazol-2-yl]-4'-[2-(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

Example 66:

(R)-2-[1-(3,5-Difluorobenzyl)-1H-imidazol-2-yl]-4'-[2-(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

Example 67:

(R)-2-[1-(2,5-Difluorobenzyl)-1H-imidazol-2-yl]-4'-[2-(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

Example 68:

(R)-2-[1-(3,4-Difluorobenzyl)-1H-imidazol-2-yl]-4'-[2-(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

Example 69:

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-[1-(2,3,6-trifluorobenzyl)-1H-imidazol-2-yl]acetanilide dihydrochloride

Example 70:

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-[1-(2,4,5-trifluorobenzyl)-1H-imidazol-2-yl]acetanilide dihydrochloride

Example 71:

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-[1-(3,4,5-trifluorobenzyl)-1H-imidazol-2-yl]acetanilide dihydrochloride

Example 72:

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-[1-(2,3,4,5,6-pentafluorobenzyl)-1H-imidazol-2-yl]acetanilide dihydrochloride

Example 73:

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-[1-(3-iodobenzyl)-1H-imidazol-2-yl]acetanilide dihydrochloride

Example 74:

(R)-2-[1-(2,6-Dichlorobenzyl)-1H-imidazol-2-yl]-4'-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide hydrochloride

Example 75:

(R)-2-[1-(4-Cyanobenzyl)-1H-imidazol-2-yl]-4'-[2-(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

Example 76:

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-[1-(quinolin-2-yl)-1H-imidazol-2-yl]acetanilide trihydrochloride

Example 77:

(R)-2-[1-(2-Chloro-6-fluorobenzyl)-1H-imidazol-2-yl]-4'-[2-(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide

Example 78:

(R)-2-[1-(2-Chloro-4-fluorobenzyl)-1H-imidazol-2-yl]-4'-[2-(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide

Example 79:

(R)-2-[1-(2,5-Dichlorobenzyl)-1H-imidazol-2-yl]-4'-[2-(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

Example 80:

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-[1-(2,3,4-trifluorobenzyl)-1H-imidazol-2-yl]acetanilide dihydrochloride

Example 81:

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-[1-(4-methoxycarbonylbenzyl)-1H-imidazol-2-yl]acetanilide dihydrochloride

Example 82:

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-[1-[(piperidine-1-carbonyl)benzyl]-1H-imidazol-2-yl]acetanilide dihydrochloride

Example 83:

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-(1-pyrazolyl)acetanilide hydrochloride

Example 84:

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-(1,2,4-triazol-1-yl)acetanilide dihydrochloride

Example 85:

(R)-2-(2-Aminobenzimidazol-1-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

Example 86:

[0098] To a solution of 20.1 g of 4'-[2-[N-benzyl-N-(2-hydroxy-2-phenylethyl)amino]ethyl]-2-(2-pyridyl)acetanilide in 400 ml of methanol was added 5.96 g of 10% palladium-carbon. The reaction solution was stirred for six hours in a

hydrogen atmosphere under atmospheric pressure. Insoluble matters were filtered off using Celite and the filtrate was concentrated in vacuo. To a methanolic solution of the resulting residue was added 10.8 ml of a 4N hydrogen chloride-ethyl acetate solution, and the solvent was evaporated in vacuo. The resulting crude crystals were recrystallized from methanol-ethanol to give (R)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]-2-(2-pyridyl)acetanilide hydrochloride.

[0099] The compounds of 87 to 90 were prepared in the same manner as in Example 86.

Example 87:

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-(3-pyridyl)acetanilide hydrochloride

Example 88:

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-(4-pyridyl)acetanilide hydrochloride

Example 89:

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-3-(2-pyridyl)propionanilide hydrochloride

Example 90:

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-[(1-phenylethyl)-1H-imidazol-2-yl]acetanilide dihydrochloride

Example 91:

[0100] (R)-2-(1H-Benzimidazol-2-yl)-4'-[4-[2-[N-benzyl-N-(2-hydroxy-2-phenylethyl)amino]ethyl]phenyl]acetanilide (240 mg) was dissolved in 30 ml of ethanol, then 170 mg of 10% palladium-carbon was added thereto and the mixture was stirred for nine hours in a hydrogen atmosphere under atmospheric pressure. The catalyst was filtered off, the solvent was evaporated in vacuo, and the residue was washed with ethanol-ethyl acetate to give 200 mg of (R)-2-(1H-benzimidazol-2-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide.

[0101] The compounds of Examples 92 and 93 were prepared in the same manner as in Example 86.

Example 92:

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-(3-methylpyridin-2-yl]acetanilide hydrochloride

Example 93:

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-(2-pyrazinyl)acetanilide hydrochloride

Example 94:

[0102] (R)-4'-[4-[2-[N-Benzyl-N-(2-hydroxy-2-phenylethyl)amino]ethyl]phenyl]-2-(1-benzyl-1H-imidazol-2-yl) acetanilide (350 mg) was dissolved in 20 ml of ethanol, then 130 mg of 10% palladium-carbon was added thereto, and the mixture was stirred for 17.5 hours in a hydrogen atmosphere under atmospheric pressure. The catalyst was filtered off, the solvent was evaporated in vacuo, and the residue was purified by silica gel column chromatography (eluent: chloroform/methanol/concentrated aqueous ammonia = 200/10/1). The resulting oily substance was dissolved in methanol, and 280 µl of a 4N hydrogen chloride-ethyl acetate solution was added thereto. The mixture was filtered after adding active carbon thereto, and the solvent was evaporated in vacuo to give 200 mg of (R)-2-(1-benzyl-1H-imidazol-2-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride.

[0103] The compounds of Examples 95 and 97 were prepared in the same manner as in Example 91; the compounds of Examples 98 and 100 were prepared in the same manner as in Example 9.4; and the compounds of Examples 99 and 101 to 103 were prepared in the same manner as in Example 86.

Example 95:

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-(4-methyl-2-pyridyl)acetanilide

Example 96:

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-(5-methyl-2-pyridyl)acetanilide

Example 97:

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-(6-methyl-2-pyridyl)acetanilide

Example 98:

4'-[(R)-2-[((R)-2-Hydroxy-2-phenylethyl)amino]propyl]-2-(2-pyridyl)acetanilide hydrochloride

Example 99:

4'-[(S)-2-[((R)-2-Hydroxy-2-phenylethyl)amino]propyl]-2-(2-pyridyl)acetanilide hydrochloride

Example 100:

2-(1-Benzyl-1H-imidazol-2-yl)-4'-[(S)-2-[((R)-2-hydroxy-2-phenylethyl)amino]propyl]acetanilide hydrochloride

Example 101:

4'-[2-[[2-Hydroxy-2-(2-fluorophenyl)ethyl]amino]ethyl]-2-(2-pyridyl)acetanilide hydrochloride

Example 102:

4'-[2-[[2-Hydroxy-2-(3-fluorophenyl)ethyl]amino]ethyl]-2-(2-pyridyl)acetanilide hydrochloride

Example 103:

4'-[2-[[2-Hydroxy-2-(4-fluorophenyl)ethyl]amino]ethyl]-2-(2-pyridyl)acetanilide hydrochloride

Example 104:

[0104] To a solution of 805 mg of 4'-cyanomethyl-2-(2-pyrimidinyl)acetanilide in 30 ml of tetrahydrofuran were added 30 ml of an ethanolic solution of Raney nickel and 3 ml of concentrated aqueous ammonia. The reaction solution was stirred for four hours in a hydrogen atmosphere under atmospheric pressure, then insoluble matters were filtered off using Celite, and the solvent was evaporated. To the resulting residue were added 10 ml of 2-propanol, 300 mg of (R)-styrene oxide and 2 ml of methanol successively. The reaction mixture was heated to reflux for ten hours, and the solvent was evaporated. The residue was purified by silica gel column chromatography (eluent: chloroform/methanol = 10/1). To a methanolic solution of the resulting residue was added 150 µl of 4N hydrogen chloride-ethyl acetate solution, and the solvent was evaporated in vacuo. The resulting residue was crystallized from methanol-ethanol-ethyl acetate and then recrystallized from ethanol-diethyl ether to give 160 mg of (R)-4'-[2-[(2-hydroxy-2-phenylethyl)amino] ethyl]-2-(2-pyrimidinyl]acetanilide hydrochloride.

[0105] The compounds of Examples 105 to 108 were prepared in the same manner as in Example 104; and the compound of Example 109 was prepared in the same manner as in Example 91.

Example 105:

(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-(2-quinolyl)acetanilide hydrochloride

Example 106:

(R)-4'-[2-[[2-Hydroxy-2-(3-chlorophenyl)ethyl]amino]ethyl]-2-(2-pyridyl)acetanilide hydrochloride

Example 107:

4'-[2-[[2-Hydroxy-2-(3-pyridyl)ethyl]amino]ethyl]-2-(2-pyridyl)acetanilide hydrochloride

Example 108:

(R)-2-[1-(4-Chlorobenzyl)-1H-benzimidazol-2-yl]-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide dihydrochloride

Example 109:

(R)-2-(4,6-Dimethyl-2-pyridyl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide

Example 110:

[0106] To 4'-(3-aminopropyl)-2-(2-pyridyl)acetanilide were added 10 ml of 2-propanol and 600 mg of (R)-styrene oxide successively. The reaction mixture was heated to reflux for four hours, and the solvent was evaporated. The residue was purified by silica gel column chromatography (eluent: chloroform/methanol = 30/1 → 10/1). To a methanolic solution of the resulting residue was added 100 µl of a 4N hydrogen chloride-ethyl acetate solution, and the solvent was evaporated in vacuo. The resulting crude crystals were recrystallized from ethanol-diethyl ether to give 71 mg of (R)-4'-[3-[(2-hydroxy-2-phenylethyl)amino]propyl]-2-(2-pyridyl)acetanilide hydrochloride.

Example 111:

[0107] To a solution of 3.62 g of tert-butyl N-[2-[4-[[2-(2-pyridyl)acetyl]amino]phenoxy]ethyl]carbamate in 30 ml of methanol was added 50 ml of a 4N hydrochloride-ethyl acetate solution. After the reaction solution was stirred at room temperature for eight hours, the solvent was evaporated in vacuo. To the residue were added an aqueous solution of sodium hydrogen carbonate and potassium carbonate to adjust to pH about 12. The resulting aqueous phase was extracted with a mixed solvent of chloroform and tetrahydrofuran. The organic layer was dried over anhydrous magnesium sulfate and concentrated, the resulting residue was dissolved in 40 ml of methanol, and 1.02 g of (R)-styrene oxide was added thereto. After the reaction solution was heated to reflux for 26 hours, the solvent was evaporated in vacuo. The resulting residue was purified by silica gel column chromatography (eluent: chloroform/methanol = 30/1 → 10/1) and dissolved in methanol, 0.59 ml of a 4N hydrogen chloride-ethyl acetate solution was added, and the solvent was evaporated in vacuo. The resulting crude crystals were recrystallized from methanol-ethanol to give 320 mg of (R)-4'-[2-[(2-hydroxy-2-phenylethyl)-amino]ethoxy]-2-(2-pyridyl)acetanilide hydrochloride

Example 112:

[0108] To a solution of 490 mg of tert-butyl N-[1,1-dimethyl-2-[4-[[2-(2-pyridyl)acetyl]amino]phenyl]ethyl]carbamate in 10 ml of methanol was added 30 ml of a 4N hydrochloride-ethyl acetate solution. After the reaction solution was stirred at room temperature for eight hours, the solvent was evaporated in vacuo. To the residue were added an aqueous solution of sodium hydrogen carbonate and potassium carbonate to adjust to pH about 12. The resulting aqueous phase was extracted with a mixed solvent of chloroform and tetrahydrofuran. The organic layer was dried over anhydrous magnesium sulfate and concentrated, the resulting residue was dissolved in 2 ml of 2-propanol and 2 ml of methanol, and 120 mg of (R)-styrene oxide was added thereto. After the reaction solution was heated to reflux for 24 hours, the solvent was evaporated in vacuo. The resulting residue was purified by silica gel column chromatography (eluent: chloroform/methanol = 30/1 → 5/1) and dissolved in methanol, 0.1 ml of a 4N hydrogen chloride-ethyl acetate solution was added, and the solvent was evaporated in vacuo. The resulting residue was purified by silica gel column chromatography (eluent: chloroform/methanol = 5/1) and reverse phase column chromatography (eluent: water/methanol = 2/1 → 1/1) to give 35 mg of (R)-4'-[2,2-dimethyl-2-[(2-hydroxy-2-phenylethyl)amino]ethyl]-2-(2-pyridyl)acetani-

lide hydrochloride.

[0109] The compound of Example 113 was prepared in the same manner as in Example 1.

Example 113:

(R)-1-[4-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]phenyl]-3-(2-pyridyl)urea dihydrochloride

[0110] Hereunder, physical and chemical properties of the compounds of the Referential Examples are given in Table 1 and those of the compounds of the Examples are given in Table 2.

[0111] The symbols in the Tables have the following meanings:

Rex.: Referential Example No.
Ex.: Example No.
DATA: Physico-chemical properties
NMR: Nucleomagnetic resonance spectrum (TMS internal standard; DMSO-d was used as a solvent unless otherwise specified)
mp: melting point
dec: decomposition
MS (m/z): mass spectrographic data (m/z)
Structure: structural formula

Table 1

Rex.	DATA
1	NMR($CDCl_3$)δ:2.75(1H,dd,J=12.4,8.8Hz),2.85-3.04(5H,m),4.70(1H,dd,J=8.8,3.7Hz),7.24-7.40(7H,m),8.10-8.20(2H,m)
2	NMR($CDCl_3$)δ:1.44(9H,s),2.75-3.10(2H,m),3.20-3.70(4H,m),4.93(1H,br),7.25-7.40(7H,m),8.14(2H,d, J=8.4Hz)
3	NMR($CDCl_3$)δ:1.47(9H,s),2.55-2.80(2H,m),3.20-3.40(2H,m),3.45-3.65(2H,m),4.87(1H,m),6.57-6.65(2H, m),6.83-7.04(2H,m),7.25-7.40(5H,m)
4	NMR($CDCl_3$)δ:1.47(9H,s),2.62-2.93(2H,m),3.14-3.58(4H,m),4.35(1H,brs),4.90(1H,br),7.06-7.40(7H,m),7.45-7.50(1H,m),7.67-7.72(2H,m),7.90(1H,dt,J=20,8.0Hz),8.25-8.31(1H,m),8.58-8.63(1H,m),9.98(1H,brs)
5	NMR($CDCl_3$)δ:1.49(9H,s),2.64-2.90(2H,m),3.16-3.60(4H,m),4.38(1H,brs),4.91(1H,br),7.10-7.42(7H,m), 7.55(1H,dd,J=8.0,4.4Hz),7.74(1H,t,J=8.0Hz),7.77-7.84(2H,m),8.01(1H,d,J=8.0,1.2Hz),8.34(1H,d, J=8.4,1.6Hz), 8.96(1H,d,J=7.6,1.6Hz),9.02(1H.d,J=4.4,2.0Hz),13.61(1H,brs)
6	NMR($CDCl_3$)δ:1.47(9H,s),2.60-2.80(2H,m),3.15-3.55(4H,m),3.78(2H,s),4.36(1H,brs),4.82-4.94(1H,m),5.18(2H,s),6.92-6.99(2H,m),7.00-7.13(5H,m),7.25-7.38(6H,m),7.42-7.48(2H,m),10.34(1H,brs)
7	NMR($CDCl_3$)δ:2.56-2.94(6H,m),3.40-3.65(2H,m),3.80(1H,brs),3.95(1H,d,13.6Hz),4.62(1H,dd, J=10.0,3.2H z),6.57-6.66(2H,m),6.87-6.98(2H,m),7.20-7.37(10H,m)
8	NMR($CDCl_3$)δ:2.40(3H,s),2.54-3.00(6H,m),3.57(1H,d,J=13.6Hz),3.88(2H,s),3.95(1H,d,J=13.6Hz),4.62 (1H ,dd,J=10.4,3.6Hz),7.00-7.75(16H.m),8.44(1H,d,J=4.4Hz),9.66(1H,brs)
9	NMR ($CDCl_3$)δ:2.58-2.65(1H,m),2.75-3.00(5H,m),3.59(1H,d,J=13.2Hz),3.95(1H,d,J=13.2Hz),5.01(1H,dd, J =10.0,3.2Hz),6.97-7.03(1H,m),7.12-7.35(9H,m),7.48-7.56(1H,m),8.04-8.13(2H,m)
10	NMR ($CDCl_3$)δ:3.70(2H,s),3.88(2H,s),7.23-7.32(4H,m),7.54-7.62(2H,m),7.71(1H,dt,J=7.6,1.6Hz),8.63 (1H, d),10.04(1H,brs)
11	NMR ($CDCl_3$)δ:2.26(3H,s),2.39(3H,s),2.57(2H,t,J=7.2Hz),2.72(2H,t,J=7.2Hz),3.72(2H,s),6.95(1H,s),7.01 (1H,s),7.11(2H,d,J=8.8Hz),7.51(2H,d,J=8.8Hz),10.17(1H,s)
12	NMRδ:2.32(3H,s),2.41(3H,s),2.90-3.19(6H,m),3.75(2H,s),4.01(2H,s),4.89(1H,dt,J=7.6,3.2Hz),6.99-7.71 (16H,m),10.26(1H,s)

Table 2

Ex.	DATA
1	mp:223-225°C, NMRδ:2.95-3.28(6H,m),4.98-5.07(1H,m),7.23-7.44(6H,m),7.65-7.75(1H,m),7.88(2H,d, J=8.4Hz),8.05-8.22(2H,m),8.75(1H,d,J=4.4Hz),8.97(1H,brs),9.43(1H,brs),10.65(1H,brs)
2	mp:263-265°C, NMRδ:2.92-3.10(3H,m),3.13-3.27(3H,m),5.00(1H,dd,J=10.8,28Hz),7.24-7.44(8H,m), 7.74-7.81(3H,m),8.57(1H,d,J=8.0Hz),8.81-8.96(2H,m),9.20-9.30(2H,m),10.71(1H,brs)
3	mp:145-147°C, NMRδ:2.94-3.10(3H,m),3.14-3.30(3H,m),4.97-5.05(1H,m),7.27-7.46(7H,m),7.77-7.90(4H, m),8.30(1H,dd,J=8.4,1,6Hz),8.60-8.71(2H,m),8.89(1H,brs),9.10-9.30(2H,m),13.12(1H.brs)
4	mp:246-248°C(dec), NMRδ:2.92-3.09(3H,m),3.11-3.26(3H,m),5.01(1H,dd,J=10.4,2.8Hz),7.24(2H,d,J=8 . 4Hz),7.29-7.47(6H,m),7.56-7.75(4H,m),7.85(1H,d,J=8.0Hz),8.11(1H,t,J=7.6Hz),8.73(1H,d,J=4.4Hz),8.92 (1H,brs),9.32(1H,brs),10.69(1H,brs)
5	mp:228-233°C(dec), NMRδ:2.88-3.09(3H,m),3.10-3.24(3H,m),4.30(2H,s),4.93-5.01(1H,m),6.19(1H,d,J= 3.6Hz),7.18-7.27(2H,m),7.28-7.53(7H,m),7.57-7.62(2H,m),7.97(1H,d,J=7,6Hz), 8.08(1H,d,J=8.0Hz),8.83 (1H ,brs),9.11(1H,brs),10.57(1H,brs)
6	mp:161-162°C, NMRδ:2.86-3.24(6H,m),4.24(2H,s),4.97(1H,dd,J=9.6,2.8Hz),7.16-7.23(2H,m),7.27-7.44 (5H,m),7.55(1H,s),7.61(2H,d,J=8.4Hz),7.85(1H,s),8.27(1H,d,J=2.4Hz),8.97(1H,brs),9.47(1H,brs),10.94 (1H, brs)
7	NMRδ:2.70(3H,s),2.86-3.27(6H,m),3,85(2H,s),5.00-5.05(1H,m),7.18-7.60(10H,m),10.43(1H,s)
8	mp:203-207°C, NMRδ:2.92-3.08(3H,m),3.10-3.22(3H,m),4.28(2H,s),5.01(1H,d,J=7.8Hz),6.21(1H,brs),7.22 (2H,d,J=8.3Hz),7.25-7.63(4H,m),8.93(1H,brs),9.38(1H,brs),10.86(1H,s)
9	mp:259-261°C, NMRδ:2.90-3.10(3H,m),3.10-3.25(3H,m),4.15(2H,s),4.97(1H,d,J=10.8Hz),6.20(1H,d, J=3.9Hz),7.21(2H,d,J=8.8Hz),7.30-7.42(5H,m),7.57(2H,d,J=8.8Hz),8.85(1H,brs),9.14(1H,brs),10.58(1H,s)
10	mp:210-213°C, NMRδ:2.86-3.08(3H,m),3.12-3.22(3H,m),3.73(2H,s),4.91-4.98(1H,m),6.19(1H,d,J=3.9Hz), 7.21(2H,d,J=8.3Hz),7.29-7.42(5H,m),7.54(2H,d,J=8.3Hz),8.78(1H,brs),8.99(1H,brs),10.35(1H,s),13.21 (1H ,brs),13.34(1H,brs)
11	mp:205-210°C(dec), NMRδ:2.90-3.25(6H,m),4.95-5.04(1H,m),7.23-7.44(7H,m),7.67-7.75(2H,m),8.15(1H, s),8.88(1H.brs),9.25(1H,brs),10.83(1H,brs)
12	mp:244-246°C, NMRδ:2.90-3.08(3H,m),3.10-3.20(3H,m),3.67(2H,s),5.00(1H,dd,J=2.4,10.02Hz),7.19(2H , d,J=8.3Hz),7.28-7.42(5H,m),7.57(2H,d,J=8.3Hz),8.90(1H,s),9.31(1H,s),10.31(1H,s)
13	mp:205-208°C, NMRδ:1.27(3H,t,J=7.1Hz),2.88-3.08(3H,m),3.12-3.22(3H,m),3.86(2H,s),4.27(2H,q, J=7.1Hz),4.96(1H,d,J=8.3Hz),6.20(1H,s),7.19(2H,d,J=8.3Hz),7.30-7.42(5H,m),7.57(2H,d,J=8.3Hz),8.81 (1H,s),9.10(1H,s),10.33(1H,s),12.53(1H,s)
14	mp:169-173°C, NMRδ:2.88-3.22(6H,m),3.66(2H,s),4.98(1H,dd,J=2.9,13.1Hz),6.72(1H,s),7.19(2H,d, J=8.3Hz),7.23-7.42(8H,m),7.59(2H,d,J=8.3Hz),7.72-7.78(1H,m),8.85(1H,s),9.18(1H,brs),10.24(1H,brs), 10.55(1H,s)
15	mp:248-251°C, NMRδ:2.90-3.08(3H,m),3.09-3.21(3H,m),3.88(2H,s),5.02(1H,dd,J=10.0,2.4Hz),6.20(1H, brs),7.16-7.22(2H,m),7.28-7.46(7H,m),7.57-7.63(2H,m),7.84(1H,t,J=7.2Hz),8.95(1H,brs),9.40(1H,brs), 10.48 (1H,brs)
16	mp:237-238°C, NMRδ:2.87-3.24(6H,m),3.77(2H,s),4.93-5.03(1H,m),5.32(2H,s),6.20(1H,d,J=4.0Hz),6.73 (1H,d,J=8.0Hz),6.99(1H,d,J=7.2Hz),7.16-7.22(2H,m),7.25-7.46(10H,m),7.57-7.63(2H,s),7.67(1H,dd, J=8.4,7 2Hz),8.87(1H,brs),9.24(1H,brs),10.30(1H,brs)
17	mp:190-193°C, NMRδ:1.68(3H,m),2.90-3.10(3H,m),3.10-3.20(3H,m),4.32(2H,s),4.67(1H,s),4.83(2H,s), 4.94(1H,s),4.99(1H,d,J=8.3Hz),6.21(1H,brs),7.21(2H,d,J=8.7Hz),7.24-7.42(5H,m),7.56(2H,d,J=8.8Hz), 7.66(2H,d,J=1.9Hz),7.71(1H,d,J=1.9Hz),8.89(1H,brs),9.30(1H,brs),10.92(1H,s)
18	mp:139-141°C, NMRδ:3.01(3H,brs),3.15(3H,brs),3.92(2H,s),5.05(1H,d,J=10.3Hz),5.44(2H,s),6.19(1H, brs),7.19(2H,d,J=8.3Hz),7.31-7.47(10H,m),7.60(2H,d,J=8.3Hz),7.66(1H,s),9.05(1H,brs),9.35(1H,s),9.60 (1H,b rs),10.76(1H,s)

Table 2 (continued)

Ex.	DATA
19	mp:140-143°C, NMRδ:2,99-3.09(3H,m),3.16(3H,brs),3.95(2H,s),5.06(1H,d,J=10.4Hz),5.57(2H,s),6.19(1H, brs),7.19(2H,d,J=8.6Hz),7.29-7.35(1H,m),7,37-7.48(8H,m),7.55-7.57(1H,m),7.61(2H,d,J=8.6Hz),9.09(1H, brs),9.31(1H,d,J=1.5Hz),9.65(1H,brs),10.79(1H,s)
20	mp:140-143°C, NMRδ:3.01-3.09(3H,m),3.16(3H,brs),3.93(2H,s),5.06(1H,d,J=10.3Hz),5.47(2H,s),6.15(1H, brs),7.19(2H,d,J=8.6Hz),7.29-7.33(1H,m),7.38-7.46(7H,m),7.61(2H,d,J=8.6Hz),7.63(1H,s),7.70(1H,s),9.0 8(1H,brs),9.38(1H,s),9.63(1H,brs),10.78(1H,s)
21	mp:141-146°C, NMRδ:2.96-3.14(3H,m),3.15(3H,brs),3.91(2H,s),5.04(1H,d,J=10.3Hz),5.45(2H,s),6.22(1H, brs),7.19(2H,d,J=8.6Hz),7.29-7.42(6H,m),7.50(3H,s),7.59(2H,d,J=8.6Hz),7.65(1H,s),9.02(1H,brs),9.32 (1H,d,J=1.5Hz),9.55(1H,brs),10.73(1H,s)
22	mp:230-235°C, NMRδ:2.59-3.10(3H,m),3.10-3.25(3H,m),4.47(2H,s),5.01(1H,dd,J=10.3,2.4Hz),5.45(2H, s),6.21(1H,brs),7.16-7.22(4H,m),7.28-7.50(7H,m),7.54(2H,d,J=8.3Hz),7.68(2H,dd,J=5.8,1.9Hz),8.94(1H, brs),9.42(1H,brs),10.98(1H,s)
.23	mp:203-209°C, NMRδ:2.90-3.10(3H,m),3.10-3.20(3H,m),4.41-4.48(2H,m),4.95-5.05(1H,m),5.46(2H,s),6 21(1H,brs),7.20(2H,d,J=8.6Hz),7.30-7.42(6H,m),7.50-7.54(2H,m),7.70(2H,s),8.92(1H,brs),9.39(1H,brs), 10. 88-10.95(1H,m)
24	mp:221-223°C, NMRδ:2.90-3.08(3H,m),3.10-3.22(3H,m),4.04(2H,s),4.97(1H,d,J=9.1Hz),5.44(2H,s),6.20 (1H,brs),7.20(2H,d,J=8.1Hz),7,30-7.41(9H,m),7.49(2H,d,J=8.6Hz),7.55(2H,d,J=8.6Hz),8.83(1H,brs),9.16 (1H,brs),10.76(1H,s)
25	mp:222-225°C, NMRδ:2.60-3.05(3H,m),3.10-3.20(3H,m),4.43(2H,s),5.01(1H,d,J=7.6Hz),5.44(2H,s),6.21 (1H,brs),7.15-7.23(4H,m),7.26-7.46(5H,m),7.51(2H,d,J=8.8Hz),7.65-7.72(4H,m),8.94(1H,brs),9.41(1H, brs), 10.93(1H,s),14.72(1H,brs)
26	mp:197-203°C, NMRδ:2.80-3.10(3H,m),3.10-3.25(3H,m),4.44(2H,s),4.99(1H,d,J=8.0Hz),5.61(2H,s),6.21 (1H,brs),7.17(2H,d,J=8.6Hz),7.30-7.42(5H,m),7.48(2H,d,J=8.5Hz),7.54(2H,d,J=8.0Hz),7.70(2H,d, J=8.1Hz), 7.72-7.77(2H,m),8.90(1H,brs),9.34(1H,brs),10.90(1H,s)
27	mp:208-214°C, NMRδ:2.90-3.10(3H,m),3.10-3.22(3H,m),4.44(2H,s),4.97(1H,d,J=9.7Hz),5.62(2H,s),6.20 (1H,brs),7.16(2H,d,J=8.0Hz),7.30-7.55(10H,m),7.70-7.94(6H,m),8.82(1H,brs),9.14(1H,brs),10.76(1H,s)
28	mp:219-223°C, NMRδ:211(3H,s),2.92-3.08(3H,m),3.10-3.20(3H,m),4.43(2H,s),5.02(1H,dd,J=10.2,2.4H z), 5.51(2H,s),6.22(1H,brs),7.14-7.34(7H,m),7.36-7.42(4H,m),7.48-7.53(3H,m),8.95(1H,brs),9.43(1H,brs),10 . 94(1H,s),14.61(1H,brs)
29	mp:204-207°C, NMRδ:2.24(3H,s),2.80-3.10(3H,m),3.10-3.50(3H,m),4.43(2H,s),5.01(1H,dd,J=10.3,2.5H z),5.39(2H,s),621 (1H,brs),7.17-724(2H,m),7.30-7.42(7H,m),7.47(2H,dd,J=8.8,5.4Hz),7.55(2H,d,J=8.3Hz), 8.94(1H,brs),9.40(1H,brs),11.00(1H,s),14.70(1H,brs)
30	mp:225-228°C, NMRδ:2.90-3.07(3H,m),3.10-3.23(3H,m),4.28(2H,s),4.97(1H,d,J=10.3Hz),5.68(2H,s),6.2 0 (1H,d,J=3.4Hz),7.16-7.23(4H,m),7.30-7.46(7H,m),7.53(2H,d,J=8.8Hz),8.82(1H,brs),9.11(1H,brs),10.63 (1H ,s)
31	mp:232-235°C, NMRδ:2.90-3.10(3H,m),3.10-3.25(3H,m),4.03(2H,s),4.98(1H,d,J=10.3Hz),5.97(2H,s),6.2 0 (1H,brs),7.19(2H,d,J=8.3Hz),7.29-7.42(6H,m),7.55(2H,d,J=8.3Hz),7.67-7.77(2H,m),8.87(1H,brs),922(1H, brs),10.49(1H,s),14.61(1H,brs)
32	mp:233-235°C, NMRδ:2.90-3.10(3H,m),3.10-3.25(3H,m),4.01(2H,s),4.98(1H,d,J=10.3Hz),5.91(2H,s),6.1 9 (1H,brs),7.17-7.48(11H,m),7.55(2H,d,J=8.3Hz),8.85(1H,brs),9.18(1H,brs),10.47(1H,s)
33	mp:240-242°C, NMRδ:2.90-3.10(3H,m),3.10-3.25(3H,m),4.32(2H,s),4.98(1H,dt,J=10.3,3.4Hz),5.72(2H,s), 6.20(1H,d,J=3.9Hz),7.20(2H,d,J=8.3Hz),7.30-7.40(6H,m),7.51(2H,d,J=8.8Hz),7.62(1H,d,J=8.3Hz),7.67 (1H,d,J=2.0Hz),8.86(1H,brs),9.17(1H,brs),10.67(1H,s)
34	mp:221-224°C, NMRδ:2.90-3.07(3H,m),3.10-3.20(3H,m),4.05(2H,s),5.00(2H,dd,J=2.7,10.2Hz),7.21(2H, d, J=8.6Hz),7.29-7.42(5H,m),7.58(2H,d,J=8.6Hz),8.83(1H,s),8.91(1H,brs),9.32(1H,brs),10.62(1H,s)
35	mp:222-224°C, NMRδ:2.89-3.07(3H,m),3.12-3.21(3H,m),3.84(2H,s),4.33(2H,s),4.98(1H,dd,J=2.4,10.2H z),7.20(2H,d,J=8.3Hz),7.22-7.42(10H,m),7.58(2H,d,J=8.3Hz),8.87(1H,brs),9.22(1H,brs),10.44(1H,s)

Table 2 (continued)

Ex.	DATA
36	mp:242-245°C, NMRδ:2.11(3H,s),2.99-3.06(3H,m),3.09-3.21(3H,m),3.68(2H,s),5.00(1H,dd,J=21,10.2H z), 6.02(1H,brs),6.98(1H,s),7.18(2H,d,J=8.1Hz),7.28-7.42(5H,m),7.58(2H,d,J=8.1Hz), 8.89(1H,brs),9.30(1H, brs),10.25(1H,s),12.10(1H,s)
37	mp:252-256°C, NMRδ:2.89(3H,s),2.91-3.07(3H,m),3.11-3.21(3H,m),3.65(2H,s),4.95-5.02(1H,m),6.20(1H, brs),6.58(1H,s),7.20(2H,d,J=8.6Hz),7.28-7.42(5H,m),7.57(2H,d,J=8.6Hz),8.87(1H,brs),9.24(1H,brs),10.3 9(1H,s), 12.56(1H,s)
38	mp:>230°C(dec.), NMRδ:2.88-3.22(6H,m),3.73(2H,s),3.65(2H,s),5.00(1H,dd,J=2.0.10.0Hz),6.20(1H,brs) , 7.12(1H,s), 7.18(2H,d,J=8.8Hz),7.28-7.42(5H,m),7.59(2H,d,J=8.8Hz),8.39(4H,brs),8.91 (1H,brs),9.32(1H, brs),10.41(1H,s),12.60(1H,s)
39	mp:177-181°C, NMRδ:2.90-3.10(3H,m),3.10-3.25(3H,m),3.67(2H,s),5.00(1H,dd,J1=10.0,20Hz),6.68(1H, s),6.97(1H,t,J=7.2Hz),7.19(2H,d,J=8.4Hz),7.27-7.42(9H,m),7.59(2H,d,J=8.0Hz),8.90(1H,brs),9.29(1H, brs) ,10.29(1H,s),10.54(1H,brs)
40	mp:237-243°C, NMR δ:2.90-3.06(3H,m),3.06-3.20(3H,m),4.45(2H,s),5.01(1H,dd,J=7.8,2.0Hz),5.70(2H,s) , 621 (1H,brs),7.14(2H,d,J=8.8Hz),7.29-7.42(5H,m),7.46(2H,d,J=8.8Hz),7.54(2H,d,J=8.8Hz),7.77(2H,dd, J=1 4.4,2.0Hz),8.13(2H,d,J=8.4Hz),8.94(1H,brs),9.41(1H,brs),10.95(1H,s)
41	mp:151-159°C, NMRδ:2.90-3.10(3H,m),3.10-3.20(3H,m),3.76(2H,s),5.02(1H,dd,J=10.2,2.7Hz),6.70(1H, s),7.20(2H,d,J=8.8Hz),7.25-7.40(5H,m),7.59(2H,d,J=8.8Hz),8.96(1H,brs),9.21(1H,brs),9.43(1H,brs),10.58 (1H,s)
42	mp:205-209°C, NMRδ:2.90-3.08(3H,m),3.13-3.23(3H,m),4.92-4.97(1H,m),6.20(1H,brs),7.19-7.42(10H, m),7.71(2H,d,J=8.8Hz),8.76(1H,brs),8.92(1H,brs),9.65(1H,s)
43	NMR δ:2.20(3H,s),2.90-3.07(3H,m),3.10-3.20(3H,m),3.74(2H,s),5.00(1H,dd,J=2.5,10.3Hz),7.20(2H,d, J=8.8Hz),7.28-7.42(5H,m),7.59(2H,d,J=8.8Hz),8.91 (1H,brs),9.13(1H,brs),9.33(1H,brs),10.58(1H,s)
44	NMR δ:1.48(6H,s),2.86-3.22(6H,m),4.90-4.96(1H,m),6.19(1H,brs),6.40(1H.brs),7.17(2H,d,J=8.8Hz), 7.27-7, 41(5H,m),7.56(2H,d,J=8.8Hz),8.74(1H,brs),8.90(1H,brs),9.53(1H,brs)
45	NMRδ:1.68-2.12(4H,m),2.43-2.59(2H,m),2.91-3.07(3H,m),3.11-3.20(3H,m),3.76-3.81(1H,m),5.00(1H,dd,J =2.5,10.3Hz),6.20(1H,brs),7.19(2H,d,J=8.3Hz),7.27-7.42(5H,m),7.60(1H,d,J=8.3Hz),8.90(1H,brs),9.33 (1H, brs),10.43(1H,s)
46	NMRδ:2.88-3.24(6H,m),3.83(2H,s),4.95-5.04(1H,m),6.19(1H,brs),7.16-7.22(2H,m),7.26-7.45(6H,m), 7.55-7 .63(2H,m),7.87(1H,s),8.04(1H,d.J=3.6Hz),8.91(1H,brs),9.32(1H,brs),10.42(1H,brs)
47	MS (m/z):456[(M+H)+], NMRδ:2.84-3.19(6H,m),4.03(2H,s),4.87-4.97(1H,m),5.43(2H,s),6.12(2H,s),7.20 (2H,d,J=8.3Hz),7.25-7.41(11H,m),7.53(2H,d,J=8.3Hz),7.90(1H,s),10.38(1H,s)
48	NMR δ:2.88-3.18(6H,m),3.69(2H,s),4.87-4.95(1H,m), 5.36(2H,s),6.15-6.21(1H,m),7.18(2H,d,J=8.3Hz), 7.27 -7.41(11H,m),7.54(2H,d,J=8.3Hz),8.57(1H,s),8.72(1H,brs),8.82(1H,brs),10.20(1H,s)
49	NMRδ:2.88-3.07(3H,m),3.11-3.21(3H,m),3.67(2H,s),4.93-4.99(1H,m),5.53(2H,s),620(1H,d,J=3.9Hz),7.00 (1H,s),7.13(2H,d,J=7.3Hz),7.18(2H,d,J=8.3Hz),7.24-7.42(8H,m),7.49(2H,d,J=8.3Hz),8.82(1H,brs),9.11 (1H,brs),10.35(1H,s)
50	NMR δ: 1.76-1.87(2H,m),2.18-2.26(2H,m),2.80-3.22(8H,m),4.39-4.47(1H,m),4.95-5.07(1H,m),7.15-7.22 (2H, m),7.27-7.43(5H,m),7.54-7.63(2H,m),7.74-7.82(1H,m),8.27(1H,d,J=7.2Hz),8.67(1H,d,J=4.8Hz),8.97 (1H,brs),9.47(1H,brs),10.74(1H,brs)
51	NMR δ: 2.90-3.10(3H,m),3.10-3.20(3H,m),4.18(2H,s),4.96(1H,d,J=8.0Hz),6.20(1H,brs),7.18(2H,d, J=8.6Hz), 7.20-7.60(12H,m),7.84(1H,s),7.97(1H,s),8.83(1H,brs),9.17(1H,brs),10.55(1H,s)
52	NMR δ: 1.14(6H,d,J=12.9Hz),2.83(1H,sep,J=12.9Hz),2.90-3.22(6H,m),4.38(2H,s),4.97(1H,d,J=4.1Hz), 5.39(2H,s),6.20(1H,brs),7.07-7.42(10H,m),7.52(2H,d,J=8.8Hz),7.67(2H,d,J=3.9Hz),8.84(1H,brs),9.17(1H, brs),10 .76(1H,s)
53	NMR δ:1.14(6H,d,J=12.9Hz),2.83(1H,sep,J=12.9Hz),2.90-3.22(6H,m),4.38(2H,s),4,97(1H,d,J=4.1Hz),5.39 (2H,s),6.20(1H,brs),7.07-7.42(10H,m),7.52(2H,d,J=8.8Hz),7.67(2H,d,J=3.9Hz),8.84(1H,brs),9.17(1H, brs),10 .76(1H,s)

Table 2 (continued)

Ex.	DATA
54	NMR δ:2.95-3.02(3H,m),3.15(3H,brs),4.44(2H,s),5.01(1H,dd,J=10.3,2.5Hz),5.58(2H,s),621 (1H,brs),7.19 (2H,d,J=8.6Hz),7.27-7.42(6H,m),7.51(2H,d,J=8.6Hz),7.58-7.60(1H,m), 7.69(1H,d,J=2.4Hz),7.72(1H,d, J=2.0Hz),7.75(1H,d,J=2.0Hz),8.96(1H,brs),9.44(1H,brs),10.91(1H,s)
55	NMR δ:2.94-3.04(3H,m),3.15(3H,brs),3.94(2H,s),5.01 (1H,d,J=10.3Hz),5.31(2H,s),6.21(1H,d,J=3.9Hz), 7.01 (1H,s),7.17-7.41(12H,m),7.54(2H,d.J=8.3Hz),8.98(1H,brs),9.35(1H,brs),10.55(1H,s)
56	NMR δ:2.95-3.05(3H,m),3.15(3H,brs),4.44(2H,s),5.01(1H,dd,J=10.3,2.5Hz),5.51(2H,s),6.20(1H,brs),7.19 (3H,d,J=8.6Hz),7.26-7.42(7H,m),7.50-7.54(3H,m),7.58(1H,d,J=20Hz),7.73(1H,d,J=2.0Hz),8.95(1H,brs), 9.43(1H,brs),10.98(1H,s)
57	NMR δ:2.92-3.05(3H,m),3.15(3H,brs),4.43(2H,s),5.01(1H,dd,J=10.2,2.6Hz),5.65(2H,s),7.20(2H,d, J=8.4Hz), 7.29-7:48(5H,m),7.50-7.53(3H,m),7.70(1H,d,J=2.0Hz),7.78(1H,d,J=2.0Hz),7.85(1H,dt, J=8.0,2.0Hz),8.49(1H,d,J=8.0Hz),8.94(1H,brs),9.42(1H,brs),10.86(1H,s)
58	mp:150-152°C, NMRδ:2.88-3.07(3H,m),3.08(3H,m),3.95(2H,s),5.00(1H,dd,J=2.8,10.0Hz),6.21(1H,s),6. 82 (1H,d,J=7.6Hz),6.91(1H,d,J=8.0Hz),7.17-7.23(2H,m),7.28-7.43(5H,m),7.55-7.62(2H,m),7.82-8.04(3H,m), 8.90(1H,brs),9.31 (1H,brs),10.67(1H.brs),14.07(1H,brs)
59	NMR δ:2.90-3.25(6H,m),4.95-5.04(1H,m), 5.20(1H,s), 622(1H,brs),6.78(1H,s),7.17-7.24(2H,m),7.27-7.44 (5H,m),7.67-7.75(2H,m),8.50-9.10(3H,br),9.45(1H,br),10.22(1H,brs)
60	mp:214-216°C,NMRδ:2.86-3.24(6H,m),3.65(2H,s),4.98(1H,dd,J-2.8,10.4Hz),6.18(1H,d,J=6.8Hz),6.28 (1H,d,J=8.8Hz),7.16-7.22(2H,m),7.28-7.45(6H,m),7.53-7.59(2H,s),8.85(1H,brs),9.18(1H,brs),10.36(1H, brs)
61	mp:180-182°C, NMRδ:0.87(6H,d,J=6.8Hz),2.05-2.15(1H,m),2.59-3.10(3H,m),3.10-3.20(3H,m),4.03(2H, d, J=7.8Hz),4.41(2H,s),5.01 (1H,d,J=8.3Hz),6.20(1H,brs),7.21(2H,d,J=8.3Hz),7.29-7.42(9H,m),7.60(2H,d,J= 8.8Hz),7.69(1H,d,J=1.9Hz),7.75(1H,d.J=2.0Hz)
62	mp:226-228°C, NMRδ:2.87-3.23(6H,m),4.45(2H,s),5.02(1H,dd,J=2.4,10.0Hz),5.55(2H,s),6.21(1H,brs),7. 16-7.46(11H,m),7.49-7.55(2H,m),7.66(1H,d,J=2.0Hz),7.71(1H,d,J=2.0Hz),8.95(1H,brs),9.44(1H,brs), 10.93(1H,brs),14.82(1H,brs)
63	mp:224-225°C, NMRδ:2.90-3.05(3H,m),3.05-3.25(3H,m),4.46(2H,s),5.01(1H,d,J=8.0Hz),5.50(2H,s),6.21 (1H,brs),7.14-7.50(11H,m),7.54(2H,d,J=8.8Hz),7.70-7.73(2H,m),8.93(1H,brs),9.39(1H,brs),10.95(1H,s)
64	mp:205-208°C, NMRδ:2.90-3.06(3H,m),3.10-3.21(3H,m),4.41(2H,s),4.99(1H,d,J=8.3Hz),5.51(2H,s),621 (1H,s),7.06-7.12(1H,m),7.20(2H,d,J=8.3Hz),7.28-7.42(6H,m),7.69(2H,dd,J=2.0,8.3Hz),8.87(1H,s),9.26 (1H, s),10.81(1H,s)
65	mp:211-216°C, NMRδ:3.00(3H,brs),3.15(3H,brs),4.44(2H,s),5.05(1H,dd,J=10.2,1.9Hz),5.58(2H,s),6.22 (1H,brs),7.14-7.22(4H,m),7.29-7.32(1H,m),7.37-7.42(4H,m),7.47-7.54(3H,m),7.65(1H,s),7.69(1H,d, J=1.9Hz) ,9.02(1H,brs),9.55(1H,brs),10.97(1H,s)
66	mp:199-201°C, NMRδ:2.87-3.23(6H,m),4.45(2H,s),4.95-5.04(1H,m),5.51(2H,s),6.20(1H,brs),7.10-7.43(1 0H,m),7.49-7.55(2H,m),7.71(1H,d,J=2.0Hz),7.74(1H,d,J=2.0Hz),8.89(1H,brs),9.30(1H,brs),10.90(1H,brs), 1 4.73(1H,brs)
67	mp:131-135°C, NMRδ:3.00(3H,brs),3.16(3H,brs),4.49(2H,s),5.04(1H,d,J=10.0Hz),5.56(2H,s),6.23(1H, brs),7.20(2H,d,J=8.2Hz),7.23-7.34(4H,m),7.37-7.42(4H,m),7.53(2H,d,J=8.2Hz),7.72(2H,s),9.01 (1H,brs), 9.54(1H,brs),11.00(1H,s)
68	mp:217-219°C, NMRδ:2.90-3.05(3H,m),3.05-3.20(3H,m),4.46(2H,s),5.00(1H,d,J=8.0Hz),5.47(2H,s),6.21 (1H,brs),7.20(2H,d,J=8.0Hz),7.25-7.50(7H,m),7.50-7.60(3H,m),7.70(1H,d,J=1.9Hz),7.71 (1H,d,J=2.0Hz), 8.9 1(1H,brs),9.33(1H,brs),10.93(1H,s)
69	mp:213-217°C, NMRδ:2.90-3.05(3H,m),3.05-3.20(3H,m),4.42(2H,s),5.02(1H,dd,J=10.2,2.4Hz),5.62(2H, s),621 (1H,brs),7.20(2H,d,J=8.3Hz),7.29-7.42(6H,m),7.49(2H,d,J=8.3Hz),7.51-7.60(1H,m), 7.68-7.73(2H, m), 8.95(1H,brs),9.42(1H,brs),10.89(1H,s)

Table 2 (continued)

Ex.	DATA
70	mp:212-213°C, NMRδ:2.87-3.23(6H,m),4.47(2H,s),5.02(1H,dd,J=2.4,10.0Hz),5.53(2H,s),6.21(1H,brs),7.16-7.23(2H,m),7.28-7.34(1H,m),7.36-7.43(4H,m),7.48-7.55(2H,m),7.57-7.67(2H,m),7.69-7.74(2H,m),8.95(1H,brs),9.43(1H,brs),10.95(1H,brs),14.86(1H,brs)
71	mp:209-213°C, NMRδ:2.90-3.05(3H,m),3.05-3.20(3H,m),4.47(2H,s),4.98-5.01(1H,m),5.49(2H,s),6.21(1H,brs),7.21(2H,d,J=8.3Hz),7.28-7.34(1H,m),7.36-7.44(6H,m),7.53(2H,d,J=8.8Hz),7.71(1H,d,J=1.9Hz),7.74(1H,d,J=1.9Hz),8.91(1H,brs),9.34(1H,brs),10.97(1H,s)
72	mp:190-193°C, NMRδ:2.90-3.08(3H,m),3.10-3.21(3H,m),4.38(2H,s),4.99(1H,dd,J=2.5,10.2Hz),5.69(2H,s),6.20(1H,s),7.21(2H,d,J=8.8Hz),7.29-7.42(5H,m),7.48(2H,d,J=8,3Hz),7.70(1H,d,J=1.9Hz),7.77(1H,s),8.88 (1H,s),9.27(1H,s),10.84(1H,s)
73	mp:233-234°C, NMRδ:2.90-3.23(6H,m),4.47(2H,s),5.02(1H,dd,J=2.4,10.0Hz),5.44(2H,s),6.21(1H,brs),7.12-7.23(3H,m),7.28-7.34(1H,m),7.36-7.44(5H,m),7.52-7.58(2H,m),7.66-7.73(3H,m),7.79-7.81(1H,m),8.96(1H,brs),9.44(1H,brs),10.96(1H.brs),14.79(1H,brs)
74	mp:180-183°C, NMRδ:2.67-2.76(4H,m),2.78-2.86(2H,m),4.00(2H,s),4.66(1H,dd,J=8.3,3.9Hz),5.39(2H,s),5.42(1H,brs),6.57(1H,d,J=0.9Hz),6.78(1H,s),7.03(2H,d,J=8.3Hz),7.21-7.26(1H,m), 7.27-7.34(4H,m), 7.46-7. 50(1H,m),7.52(2H,d,J=8.3Hz),7.56(1H,s),7.58(1H,s), 8.32(1H,s),10.32(1H,s)
75	mp:210-215°C, NMRδ:2.91-3.03(3H,m),3.15(3H,brs),4.44(2H,s),5.01(1H,dd,J=10.4,2.6Hz),5.53(2H,s),6.21(1H,brs),7.18(2H,d,J=8.3Hz),7.30-7.32(1H,m),7.37-7.42(4H,m),7.48(2H,d,J=8.3Hz),7.49(2H,d,J=8.3Hz), 7.74(1H,d,J=2.0Hz),7.75(1H,d,J=2.0Hz),7.79(2H,d,J=8.3Hz),8.94(1H,brs),9.39(1H,brs),10.93(1H,s)
76	mp:162-165°C, NMRδ:2.93-3.05(3H,m),3.14(3H,brs),4.47(2H,s),5.03(1H,dd,J=10.3,2.5Hz),5.62(1H,brs),5.89(2H,s),7.12(2H,d,J=8.3Hz),7.30-7.37(1H,m),7.39-7.43(6H,m),7.61(2H,d,J=8.8Hz),7.69(1H,t,J=7.5Hz),7 .75(1H,d,J=1.9Hz),7.83-7.86(2H,m),7.97(1H,d,J=8.3Hz),8.44(1H,d,J=8.3Hz),8.99(1H,brs),9.52(1H,brs),10.8 4(1H,s)
77	NMR δ:2.64-2.74(4H,m),2.77-2.82(2H,m),3.93(2H,s),4.63(1H,dd,J=7.8,4.4Hz),5.33(2H,s),6.80(2H,d,J=6.3Hz),7.14(2H,d,J=8.8Hz),7.20-7.24(1H,m),7.28-7.35(5H,m),7.43(1H,d,J=7.8Hz),7.47-7.52(3H,m),10.27(1H,s)
78	NMRδ:2.63-2.72(4H,m),2.75-2.81(2H,m),3.79(2H,s),4.62(1H,dd,J=7.8,4.4Hz),5.30(1H,brs),5.33(2H,s),6.68(1H,d,J=1.0Hz),6.91(1H,dd,J=8.8,5.9Hz),7.06(1H,d,J=1.0Hz),7.12(2H,d,J=8.8Hz),7.19-7.24(2H,m),7:28-7. 33(4H,m),7.43(2H,d,J=8,3Hz),7.49(1H,dd,J=8.3,2.5Hz),8.32(1H,s),10.21(1H,s)
79	NMR δ:2.88-3.08(3H,m),3.10-3.22(3H,m),4.40(2H,s),4.97(1H,d,J=8.3Hz),5.56(2H,s),6.20(1H,s),7.19(2H,d, J=8.3Hz),7.24(1H,d,J=2.5Hz),7.30-7.60(9H,m),7.64(1H,d,J=2.0Hz),7.72(1H,s),8.83(1H,s),9.14(1H,s), 10.71 (1H,s)
80	NMRδ:2.90-3.08(3H,m),3.10-3.22(3H,m),4.44(2H,s),5.02(1H,d,J=8.8Hz),5.59(2H,s),6.21(1H,s),7.20(2H,d,J=8.0Hz),7.24-7.42(7H,m),7.50(2H,d,J=8.8Hz),7.72(2H,d,J=6.8Hz),8.94(1H,s),9.42(1H,s),10.93(1H,s)
81	NMRδ:2.87-3.23(6H,m),3.85(3H,s),4.30(2H,s),4.94-5.01(1H,m),5.55(2H,s),6.17-6.22(1H,br),7.14-7.23(2H,m), 7.28-7.50(9H,m),7.57-7.64(2H,m),7.87-7.93(2H,m),8.83(1H,brs),9.10(1H,brs),10.68(1H,brs),14.86(1H,brs)
82	NMRδ:1.30-1.64(6H,m),2.88-3.22(8H,m),3.45-3.65(2H,m),4.39(2H,s),4.97(1H,d,J=9.8Hz),5.50(2H,s),6.21(1H,s),7.20(2H,d,J=8.3Hz),7.30-7.42(9H,m),7.51(2H,d,J=8.7Hz),7.71(2H,d,J=7.8Hz),8.81(1H,s),9.14(1H,s), 10.77(1H,s)
83	mp:229-232°C, NMRδ:2.90-3.00(3H,m),3.10-3.18(3H,m),5.00(1H,dd,J=2.8,10.1Hz),5.03(2H,s),6.27(1H,t J=2.0Hz),7.20(2H,d,J=8.8Hz),7.29-7.42(5H,m),7.46(1H,d,J=2.4Hz),7.58(2H,d,J=8.8Hz),7.77(1H,d, J=2.0Hz),8.91(1H,s),9.32(1H,s),10.53(1H,s)
84	mp:237-240°C, NMRδ:2.90-3.08(3H,m),3.10-3.22(3H,m),4.96(1H,dd,J=20,10.0Hz),5.15(2H,s),7.21(2H, d, J=8.0Hz),7.28-7.42(5H,m),7.56(2H,d,J=8.4Hz),8.03(1H,s),8.61 (1H,s),8.82(1H,s),9.09(1H,s),10.57(1H,s)
85	mp:244-248°C, NMRδ:2.90-3.06(3H,m),3.10-3.20(3H,m),5.00(1H,d,J=7.6Hz),5.20(2H,s),6.20(1H,s),7.20-7.50(11H,m),7.59(2H,d,J=7.2Hz),8.94(3H,s),9.36(1H,s),10.95(1H,s),12.92(1H,s)

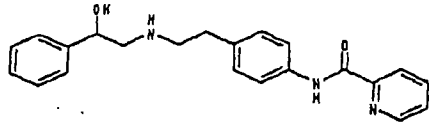
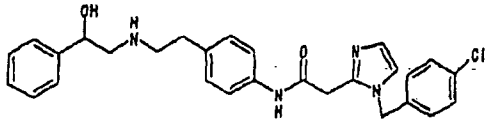
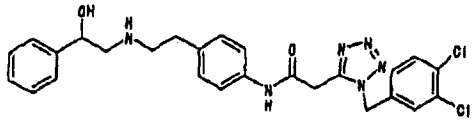
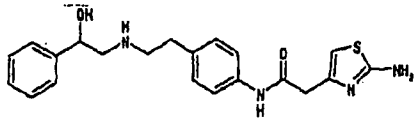
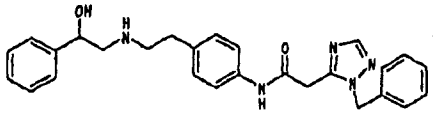
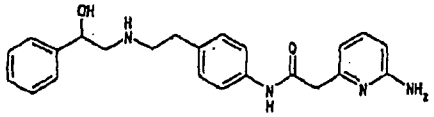
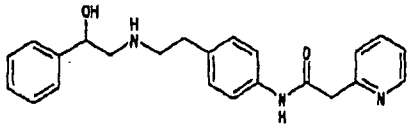
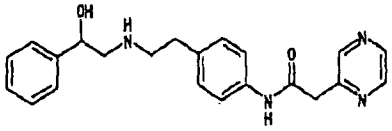
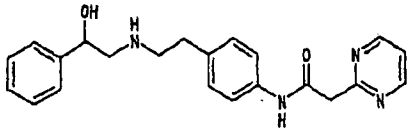
Table 2 (continued)

Ex.	DATA
86	mp:223-224°C, NMRδ:2.86-3.22(6H,m),3.49(2H,s),4.93-5.03(1H,m),6.20(1H,d,J=4.0Hz),7.15-7.43(9H, m),7.55-7.62(2H,m),7.75(1H,dt,J=1.6,8.0Hz),8.45-8.53(1H,m), 8.06-9.50(2H,br),10.35(1H,brs)
87	mp:236-238°C, NMRδ:2.86-3.23(6H,m),3.72(2H,s),4.91-5.02(1H,m),6.20(1H,d,J=4.0Hz),7.15-7.22(2H, m),7.27-7.45(6H,m),7.53-7.62(2H,m),7.73-7.82(1H,m),8.40-8.60(2H,m),8.84(1H,brs),9.16(1H,brs), 10.35-10.5 0(1H,br)
88	mp:195-198°C, NMRδ:2.86-3.22(6H,m),3.73(2H,s),4.93-5.04(1H,m),6.15-6.25(1H,br),7.14-7.22(2H,m),7 . 28-7.43(7H,m),7.54-7.63(2H,m),8.47-8.53(2H,m),9.07(2H,brs),10.50(1H,brs)
89	mp:202-204°C, NMRδ:2.71-2.81(2H,m),2.88-3.24(8H,m),3.49(2H,s),4.93-5.05(1H,m),6.20(1H,brd, J=3.2Hz),7.15-7.23(3H,m),7.26-7.44(6H,m),7.52-7.60(2H,m),7.69(1H,dt,J=1.6,7.6Hz),8.45-8.51(1H,m), 9.07(2H, brs),10.07(1H,brs)
90	mp:220-227°C, NMRδ:2.80-3.20(8H,m),4.31(2H,s),4.42(2H,t,J=8.0Hz),5.00(1H,d,J=1.0Hz),6.21(1H,brs), 7.20-7.40(12H,m),7.59(2H,d,J=8.6Hz),7.65(2H,dd,J=12.9,0.9Hz),8.91(1H,brs),9.34(1H,brs),10.98(1H,s)
91	mp:158-165°C, NMRδ:2.51-2.78(6H,m),3.96(2H,s),4.59(1H,t,J=5.2Hz),5.20(1H,brs),7.13-7.32(9H,m),7.5 0-7.53(4H,m),10.33(1H,s),12.37(1H,brs)
92	mp:216-217°C, NMRδ:2.31(3H,s),2.86-3.24(6H,m),3.89(2H,s),4.92-5.07(1H,m),6.20(1H,d,J=4.0Hz),7.12 -7.22(3H,m),7.28-7.45(5H,m),7.50-7.64(2H,m),8.30(1H,d,J=4.4Hz),8.60-9.50(2H,br0,10.32(1H,brs)
93	mp:236-238°C, NMRδ:2.86-3.24(6H,m),3.95(2H,s),4.91-5.01(1H,m),5.44(2H,s),6.19(1H,d,J=4.4Hz),7.15 -7.22(2H,m),7.27-7.43(5H,m),7.52-7.62(2H,m),8.50-8.69(3H,m),8.83(1H,br),9.12(1H,brs),10.41(1H,brs)
94	NMR δ:2.90-3.10(3H,m),3.10-3.20(3H,m),4.38(2H,s),4.98(1H,t,J=10.4Hz),5.44(2H,s),6.20(1H,d,J=3.2Hz), 7 .20(2H,d,J=8.4Hz),7.30-7.45(9H,m),7.53(2H,d,J=8.8Hz),7.64(2H,s),8.85(1H,brs),921 (1H,brs),10.79(1H, s)
95	NMRδ:2.31(3H,s),2.89-3.17(6H,m),3.79(2H,s),4.98(1H,dt,J=3.2,10.4Hz),7.10-7.41(12H,m),10.32(1H,s)
96	NMRδ:2.27(3H,s),2.89-3.17(6H,m),3.79(2H,s),4.99(1H,dt,J=3.6,10.0Hz),7.17-7.59(12H,m).10.31(1H,s)
97	NMRδ:2.44(3H,s),2.78-3.20(6H,m),3.80(2H,s),4.97(1H,dt,J=3.2,10.4Hz),7.12-7.66(12H,m),10.33(1H,s)
98	NMR δ:1.06(3H,d,J=6.4Hz),2.50-2.65(2H,m),2.90-3.15(3H,m),3.83(2H,s),4.80-4.94(1H,m),7.10-7.18(2H, m) ,7.23-7.45(7H,m),7.52-7.60(2H,m),7.71-7.80(1H,m),8.41-8.52(1H,m),10.25(1H,brs)
99	mp:203-204°C, NMRδ:1.13(3H,d,J=6.4Hz),2.55-2.64(1H,m),3.00-3.50(4H,m),3.84(2H,s),4.92-5.02(1H, m),6.20(1H,d,J=4.0Hz),7.13-7.20(2H,m),7.24-7.46(7H,m),7.54-7.60(2H,m),7.73-7.80(1H,m),8.51(1H,brs), 8.6 7(1H,brs),9.13(1H,brs),10.31(1H,brs)
100	NMRδ:1.06(3H,d,J=6.4Hz),2.50-2.65(1H,m), 2.57-3.50(4H,m),3.78(2H,s),4.77-4.92(1H,m),5.25(2H,s),6.85 (1H,s),7.10-7.55(15H,m),10.33(1H,brs)
101	mp:194-196°C, NMRδ:2.88-3.25(6H,m),3.89(2H,s);5.20-5.26(1H,m),6.30(1H,s),7.17-7.48(7H,m),7.54-7. 60(3H,m),7.81-7.88(1H,m),8.54(1H,d,J=4.0Hz),8.82(1H,s),9.16(1H,s),10.35(1H,s)
102	mp:214-215°C, NMRδ:2.88-3.25(6H,m),3.85(2H,s),4.96-5.02(1H,m),6.33(1H,d,J=3.8Hz),7.12-7.31(6H, m),7.39-7.48(2H,m),7.58(2H,d,J=8.3Hz),7.74-7.80(1H,m),8.50(1H,s),8.82(1H,s),9.01(1H,s),10.30(1H,s)
103	mp:223-225°C, NMRδ:2.88-3.06(3H,m),3.10-3.20(3H,m),3.84(2H,s),4.94-5.01(1H,m),6.24(1H,d, J=4.0Hz),7.16-7.30(5H,m),7.38-7.46(3H,m),7.58(2H,d,J=8.8Hz),7.76(1H,dt,J=1.6,7.6Hz),8.5)(1H,d, J=8.8Hz),8.83(1Hs),9.08(1H,s),10.31(1H,s)
104	mp:208-210°C, NMRδ:2.88-3.24(6H,m),3.99(2H,s),4.90-5.01(1H,m),6.20(1H,d,J=3.6Hz),7.15-7.24(2H, m),7.28-7.44(6H,m),7.53-7.62(2H,m)8.50-9.30(4H,m),10.33(1H,brs)
105	mp:234-235°C, NMRδ:2.94-3.25(6H,m),4.07(2H,s),4.90-5.02(1H,m),6.20(1H,d,J=4.0Hz),7.16-7.23(2H, m),7.27-7.44(5H,m),7.53-7.65(4H,m),7.71-7.78(1H,m), 7.94-8.00(2H,m),8.33(1H,d,J=8.0Hz),8.50-9.25 (2H,m), 10.46(1H,brs)

Table 2 (continued)

Ex.	DATA
106	mp:221-222°C, NMRδ:2.90-3.25(6H,m),3,85(2H,s),4.92-5.08(1H,m),6.35(1H,d,J=3.6Hz),7.14-7.23(2H, m),7.23-7.31(1H,m), 7.33-7.50(5H,m),7.54-7.64(2H,m),7.76(1H,dt,J=1.6,7.6Hz),8.43-8.55(1H,m), 8.80-9.40(2H,br),10.36(1H,brs)
107	mp:204-205°C, NMRδ:2.85-3.28(6H,m),3.85(2H,s),5.02-5.14(1H,m),6.37(1H,d,J=4.0Hz),7.14-7.32(3H, m),7.36-7.46(2H,m),7.55-7.64(2H,m),7.70-7.86(2H,m),8.46-8.56(2H,m),8.57-8.65(1H,m),9.13(2H,brs), 10.37(1H,brs)
108	NMR δ:2.63-2.67(4H,m),2.73-2.78(2H,m),4.07(2H,s),4.60(1H,dd,J=7.4,4.9Hz),5.24(1H,brs),5.57(2H,s), 7.12 -7.23(7H,m),7.27-7.31(4H,m),7.37(3H,d,J=8.3Hz),7.46(2H,d,J=8.3Hz),7.60-7.61(1H,m),8.31(1H,s), 10.31(1H ,s)
109	NMR δ:226(3H,s),2.40(3H,s),2.90-3.17(6H,m),3.75(2H,s),4.99(1H,dt,J=3.2,6.8Hz),6.97-7.60(11H,m),10.3 5(1H,s)
110	mp:183-184°C, NMRδ:1.85-2.05(2H,m),2.53-2.65(2H,m),2.83-3.03(3H,m),3.05-3.16(1H,m),3.88(2H,s),4 . 95(1H,d,J=9.6Hz),6.15(1H,brs),7.10-7.18(2H,m),7.22-7.43(7H,m),7.50-7.60(2H,m),7.75(1H,dt, J=1.6,7.2Hz),8.45-8.53(1H,m),8.91(2H,brs),10.29(1H,brs)
111	mp:225-226°C, NMRδ:3.02-3.14(1H,m),3.18-3.46(3H,m),3.84(2H,s),4.22-4.35(2H,m),4.98-5.08(1H,m),6 21 (1H,d,J=3.6Hz),6.90-6.97(2H,m),7.23-7.44(7H,m),7.53-7.62(2H,m),7.76(1H,dt,J=1.6,7.2Hz),8.45-8.54 (1H,m),8.80-9.50(2H,br),10.29(1H.brs)
112	NMR δ:1.21(6H,s),2.85-3.23(4H,m),3.89(2H,s),4.90-5.00(1H,m),621 (1H,brs),7.11-7.19(2H,m),7.28-7.50 (7H,m),7.53-7.62(2H,m),7.78-7.90(1H,m),8.45-8.60(2H,m),9.00-9.10(1H,br),10.35(1H,brs)
113	mp:132-133°C, NMRδ:2.90-3.10(3H,m),3.13-3.23(3H,m),4.96(1H,dd,J=2.5,10.2Hz),7.06-7.11(1H,m,),7. 21 (2H,d,J=8.7Hz),7.30-7.42(5H,m),7.47-7.53(3H,m),7.81-7.87(1H,m),8.29(1H,d,J=4.9Hz),8.78(1H,s),9.00 (1H,s),9.88(1H,s),10.51(1H,s)

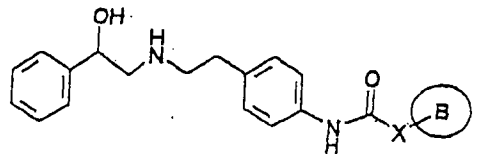
Table 3

Ex.	Structure
1	
23	
33	
41	
47	
58	
86	
93	
104	

[0112] Table 3 gives the structural formulae for some Examples.

[0113] The compounds shown in Tables 4 and 5 together with chemical structural formulae can be easily manufactured by almost the same method as mentioned in the above Examples or Manufacturing Methods or by such method to which some modifications known to the persons skilled in the art are applied. In some cases, there are tautomeric, geometric or optical isomers for the compounds mentioned in Tables 4 and 5, and the compounds of the present invention cover each of the isolated isomers and a mixture thereof.

Table 4



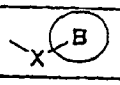
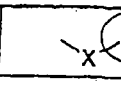
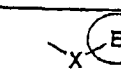
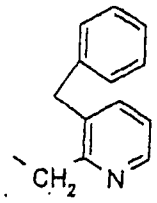
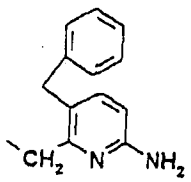
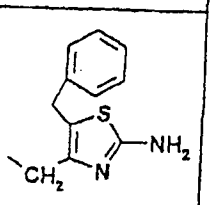
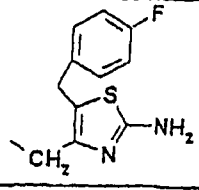
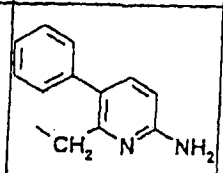
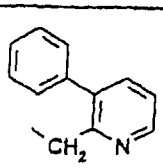
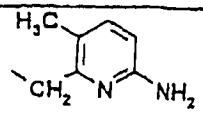
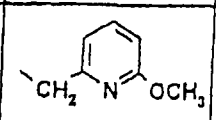
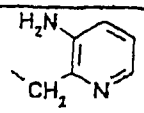
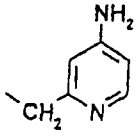
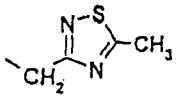
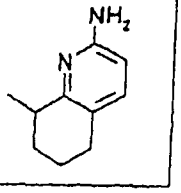
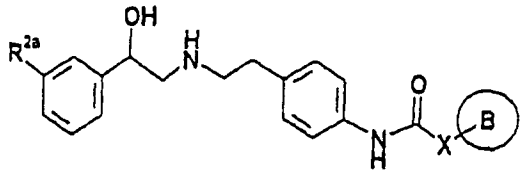
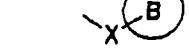
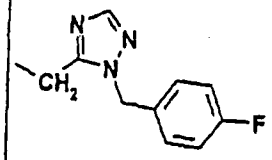
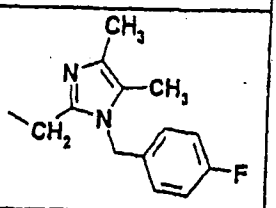
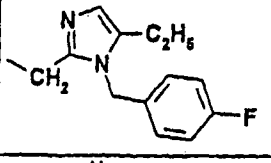
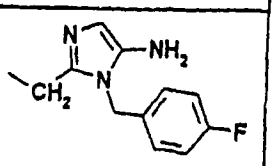
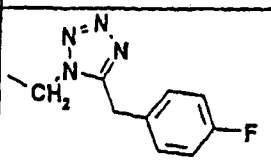
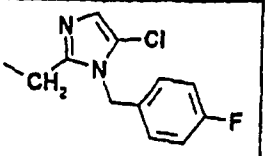
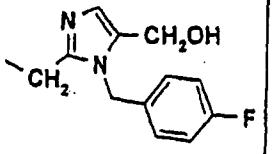
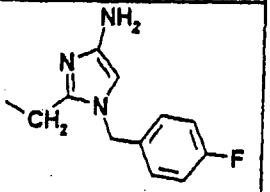
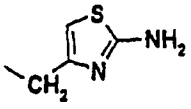
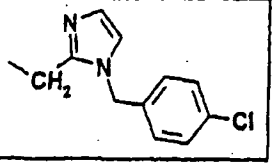
No.		No.		No.	
1		2		3	
4		5		6	
7		8		9	
10		11		12	

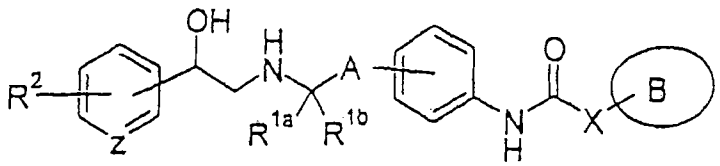
Table 5



No.	R^{2a}		No.	R^{2a}	
13	H		14	H	
15	H		16	H	
17	H		18	H	
19	H		20	H	
21	Cl		22	Cl	

Claims

1. An amide derivative of formula (I) or a salt thereof:



(I)

wherein

ring B is an optionally fused heteroaryl group selected from imidazothiazol, thioxothiazol, tetrahydrobenzothiazol, tetrahydroquinolinyl, quinolyl, isoquinolyl, quinazolinyl, quinolidinyl, quinoxalinyl, cinnolinyl, benzimidazolyl, imidazopyridyl, benzoisoxazolyl, benzoxazolyl, benzothiazolyl, oxazolopyridyl, isothiazolopyridyl, pyrrolyl, imidazolyl, thiazolyl, pyrazolyl, isothiazolyl, isoxazolyl, pyridyl, pyrimidyl, pyridazinyl, pyrazinyl, thiadiazolyl, triazolyl, tetrazolyl, naphthyridinyl and pyridopyrimidinyl groups, which heteroaryl group may be substituted with at least one substituent selected from halogens and C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, hydroxy, sulfanyl, halogeno C_1-C_6 alkyl, C_1-C_6 alkyl-O-, C_1-C_6 alkyl -S-, C_1-C_6 alkyl-O-CO-, carboxy, sulfonyl, sulfinyl,C_1-C_6 alkyl-SO-, C_1-C_6 alkyl-SO_2-, C_1-C_6 alkyl-CO-, C_1-C_6 alkyl-CO-O-, carbamoyl, C_1-C_6 alkyl-NH-CO-, di-C_1-C_6 alkyl-N-CO-, nitro, cyano, amino, C_1-C_6 alkyl-NH-, di-C_1-C_6 alkyl-N-, benzyl, halogenobenzyl, cyanobenzyl, nitrobenzyl, trifluoromethylbenzyl, isopropylbenzyl, phenylbenzyl, methoxycarbonylbenzyl, piperidinecarbonyl benzyl, benzyloxy, benzylsulfanyl, phenylamino, fluorophenylamino, phenylethyl, phenyl, naphthyl, quinolinyl, pyridylmethyl, guanidino, C_1-C_6 alkyl-CO-NH - and C_1-C_6 alkyl-SO_2-NH- groups;

X is a bond; a C_1-C_6 alkylene or C_2-C_6 alkenylene group which may be substituted with a hydroxy or C_1-C_6 alkyl group; a carbonyl group; or -NH-; with the proviso that when X is a C_1-C_6 alkylene group optionally substituted with a C_1-C_6 alkyl group it may form a ring together with carbon atoms of ring B;

A is methylene, ethylene, or $-CH_2O-$;

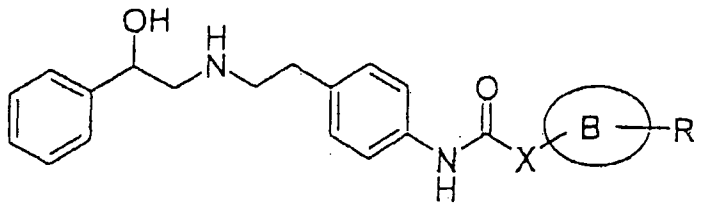
R^{1a} and R^{1b} are the same or different and selected from H and C_1-C_6 alkyl groups;

R^2 is H or halogen; and

Z is a N or =CH-.

2. A compound according to claim 1 wherein R^2, R^{1a} and R^{1b} are each a H, and Z is =CH-.

3. A compound according to claim 1 which is an amide derivative of formula (Ia) or a salt thereof:



(Ia)

wherein

ring B is a heteroaryl group as defined in claim 1;

X is a bond or a C_1-C_6 alkylene group; and

R is H or halogen or a C_1-C_6 alkyl, amino, benzyl or halogenobenzyl group.

4. A compound according to claim 1 selected from

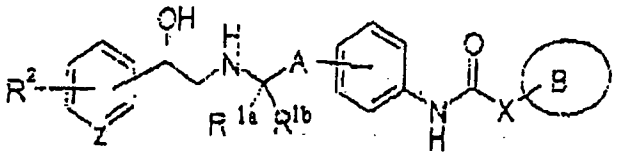
(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-pyridinecarboxanilide, (R)-2-[1-(4-chlorobenzyl)-1H-imidazol-2-yl]-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]-acetanilide, (R)-2-[1-(3,4-dichlorobenzyl)-1H-tetrazol-5-yl]-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide, (R)-2-(2-aminothiazol-4-yl)-4'-[2-(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide, (R)-2-(1-benzyl-1H-1,2,4-triazol-5-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide, (R)-2-(2-aminopyridin-6-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide, (R)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]-2-(2-pyridyl)acetanilide, (R)-4'-[2-[(2-hydroxy-2-phenylethyl)-amino]ethyl]-2-(2-pyrazinyl)acetanilide, (R)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]-2-(2-pyrimidinyl)-acetanilide, and salts thereof.

5. A pharmaceutical composition containing a compound according to any preceding claim.

6. The use of a compound according to any of claims 1 to 4 for the preparation of a medicament for treating diabetes mellitus.

Patentansprüche

1. Amidderivat der Formel (I) oder ein Salz davon:



(I)

wobei

Ring B eine optional fusionierte Heteroarylgruppe ist, ausgewählt aus Imidazothiazol-, Thioxothiazol-, Tetrahydrobenzothiazol-, Tetrahydrochinolinyl-, Chinolyl-, Isochinolyl-, Chinazolinyl-, Chinolidinyl-, Chinoxalinyl-, Cinnolinyl-, Benzimidazolyl-, Imidazopyridyl-, Benzoisoxazolyl-, Benzoxazolyl-, Benzothiazolyl-, Oxazolopyridyl-, Isothiazolopyridyl-, Pyrrolyl-, Imidazolyl-, Thiazolyl-, Pyrazolyl-, Isothiazolyl-, Isoxazolyl-, Pyridyl-, Pyrimidyl-, Pyridazinyl-, Pyrazinyl-, Thiadiazolyl-, Triazolyl-, Tetrazolyl-, Naphthyridinyl- und Pyridopyrimidinylgruppen, wobei die Heteroarylgruppe substituiert sein kann durch wenigstens einen Substituenten, ausgewählt aus Halogenen und C_1-C_6-Alkyl-, C_2-C_6-Alkenyl-, C_2-C_6-Alkynyl-, Hydroxy-, Sulfanyl-, Halogeno-C_1-C_6-Alkyl-, C_1-C_6-Alkyl-O-, C_1-C_6-Alkyl-S-, C_1-C_6-Alkyl-O-CO-, Carboxy-, Sulfonyl-, Sulfinyl-, C_1-C_6-Alkyl-SO-, C_1-C_6-Alkyl-SO_2-, C_1-C_6-Alkyl-CO-, C_1-C_6-Alkyl-CO-O-, Carbamoyl-, C_1-C_6-Alkyl-NH-CO-, di-C_1-C_6-Alkyl-N-CO-, Nitro-, Cyano-, Amino-, C_1-C_6-Alkyl-NH-, di-C_1-C_6-Alkyl-N-, Benzyl-, Halogenobenzyl-, Cyanobenzyl-, Nitrobenzyl-, Trifluormethylbenzyl-, Isopropylbenzyl-, Phenylbenzyl-, Methoxycarbonylbenzyl-, Piperidincarbonylbenzyl-, Benzyloxy-, Benzylsulfanyl-, Phenylamino-, Fluorphenylamino-, Phenylethyl-, Phenyl-, Naphthyl-, Chinolinyl-, Pyridylmethyl-, Guanidino-, C_1-C_6-Alkyl-CO-NH- und C_1-C_6-Alkyl-SO_2-NH-Gruppen;

X Folgendes ist: eine Bindung; eine C_1-C_6-Alkylenoder C_2-C_6-Alkenylengruppe, die substituiert sein kann durch eine Hydroxy- oder C_1-C_6-Alkylgruppe; eine Carbonylgruppe; oder -NH-; unter der Voraussetzung, dass, wenn X eine C_1-C_6-Alkylengruppe ist, die optional substituiert ist durch eine C_1-C_6-Alkylgruppe, es zusammen mit Kohlenstoffatomen von Ring B einen Ring bilden kann;

A Methylen, Ethylen oder -CH_2-O- ist;

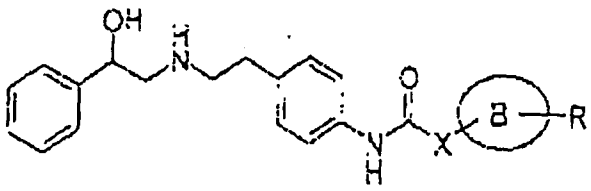
R^{1a} und R^{1b} gleich oder unterschiedlich sind und ausgewählt sind aus H und C_1-C_6-Alkylgruppen;

R^2 H oder Halogen ist; und

Z N oder =CH- ist.

2. Verbindung nach Anspruch 1, wobei R^2, R^{1a} und R^{1b} jeweils H sind und Z =CH- ist.

3. Verbindung nach Anspruch 1, die ein Amidderivat der Formel (Ia) oder ein Salz davon ist:



(Ia)

wobei

Ring B eine Heteroarylgruppe gemäß Definition in Anspruch 1 ist;

X eine Bindung oder eine C_1-C_6-Alkylengruppe ist; und

R H oder Halogen oder eine C_1-C_6-Alkyl-, Amino-, Benzyl- oder Halogenobenzylgruppe ist.

4. Verbindung nach Anspruch 1, ausgewählt aus (R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-pyridincar-

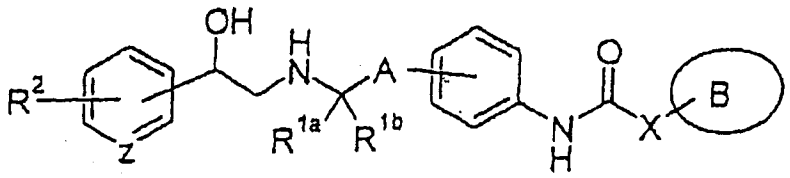
boxanilid, (R)-2-[1-(4-Chlorbenzyl)-1Himidazol-2-yl]-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]-acetanilid, (R)-2-[1-(3,4-Dichlorbenzyl)-1H-tetrazol-5-yl]-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilid, (R)-2-(2-Aminothiazol-4-yl)-4'-[2-(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilid, (R)-2-(1-Benzyl-1H-1,2,4-trizaol-5-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilid, (R)-2-(2-Aminopyridin-6-yl)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]acetanilid,(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-(2-pyridyl)acetanilid,(R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-(2-pyrazinyl)acetanilid, (R)-4'-[2-[(2-Hydroxy-2-phenylethyl)amino]ethyl]-2-(2-pyrimidinyl)-acetanilid und Salzen davon.

5. Pharmazeutische Zusammensetzung, die eine Verbindung nach einem der vorherigen Ansprüche enthält.

6. Verwendung einer Verbindung nach einem der Ansprüche 1 bis 4 zur Herstellung eines Medikamentes zur Behandlung von Diabetes mellitus.

Revendications

1. Dérivé amide de la formule (I) ou un sel de celui-ci :



(I)

où

le cycle B est un groupe hétéroaryle optionnellement fusionné sélectionné parmi les groupes imidazothiazole, thioxothiazole, tétrahydrobenzothiazole, tétrahydroquinolinyle, quinolyle, isoquinolyle, quinazolinyle, quinolidinyle, quinoxalinyle, cinnolinyle, benzimidazolyle, imidazopyridyle, benzoisoxazolyle, benzoxazolyle, benzothiazolyle, oxazolopyridyle, isothiazolopyridyle, pyrrolyle, imidazolyle, thiazolyle, pyrazolyle, isothiazolyle, isoxazolyle, pyridyle, pyrimidyle, pyridazinyle, pyrazinyle, thiadiazolyle, triazolyle, tétrazolyle, naphtyridinyle et pyridopyrimidinyle, lequel groupe hétéroaryle peut être substitué avec au moins un substituant sélectionné parmi des halogènes et des groupes alkyle C_1-C_6, alcényle C_2-C_6, alkynyle C_2-C_6, hydroxy, sulfanyle, halogéno-alkyle C_1-C_6, alkyl-C_1-C_6-O-, alkyl-C_1-C_6-S-, alkyl-C_1-C_6-O-CO-, carboxy, sulfonyle, sulfinyle, alkyl-C_1-C_6-SO-, alkyl-C_1-C_6-SO_2-, alkyl-C_1-C_6-CO-, alkyl-C_1-C_6-CO-O-, carbamoyle, alkyl-C_1-C_6-NH-CO-, dialkyl-C_1-C_6-N-CO-, nitro, cyano, amino, alkyl-C_1-C_6-NH-, dialkyl-C_1-C_6-N-, benzyle, halogénobenzyle, cyanobenzyle, nitrobenzyle, trifluorométhylbenzyle, isopropylbenzyle, phénylbenzyle, méthoxycarbonylbenzyle, pipéridinecarbonylbenzyle, benzyloxy, benzylsulfanyle, phénylamino, fluorophénylamino, phényléthyle, phényle, naphtyle, quinolinyle, pyridylméthyle, guanidino, alkyl-C_1-C_6-CO-NH- et alkyl-C_1-C_6-SO_2-NH-;

X est une liaison; un groupe alkylène C_1-C_6 ou un groupe alcénylène C_1-C_6 qui peut être substitué avec un groupe hydroxy ou alkyle C_1-C_6; un groupe carbonyle; ou -NH-; à condition que lorsque X est un groupe alkylène C_1-C_6 optionnellement substitué avec un groupe alkyle C_1-C_6, il puisse former un cycle avec des atomes de carbone du cycle B;

A est un méthylène, un éthylène, ou -CH_2O-;

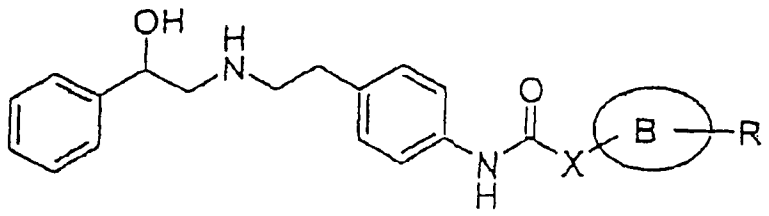
R^{1a} et R^{1b} sont les mêmes ou différents et sont sélectionnés parmi H et des groupes alkyle C_1-C_6;

R^2 est H ou un halogène; et

Z est un N ou =CH-.

2. Composé selon la revendication 1, dans lequel R^2, R^{1a} et R^{1b} sont chacun un H, et Z est =CH-.

3. Composé selon la revendication 1, qui est un dérivé amide de la formule (Ia) ou un sel de celui-ci :



(Ia)

où

le cycle B est un groupe hétéroaryle tel que défini dans la revendication 1;
X est une liaison ou un groupe alkylène C_1-C_6; et
R est H ou un halogène ou un groupe alkyle C_1-C_6, amino, benzyle ou halogénobenzyle.

4. Composé selon la revendication 1, sélectionné parmi le (R)-4'-[2-[(2-hydroxy-2-phényléthyl)amino]éthyl]-2-pyridinecarboxanilide, le (R)-2-[1-(4-chlorobenzyl)-1H-imidazol-2-yl]-4'-[2-[(2-hydroxy-2-phényléthyl)amino]éthyl]-acétanilide, le (R)-2-[1-(3,4-dichlorobenzyl)-1H-tétrazol-5-yl]-4'-[2-[(2-hydroxy-2-phényléthyl)amino]éthyl]-acétanilide, le (R)-2-(2-aminothiazol-4-yl)-4'-[2-(2-hydroxy-2-phényléthyl)amino]éthyl]acétanilide, le (R)-2-(1-benzyl-1H-1,2,4-triazol-5-yl)-4'-[2-[(2-hydroxy-2-phényléthyl)amino]éthyl]-acétanilide, le (R)-2-(2-aminopyridin-6-yl)-4'-[2-[(2-hydroxy-2-phényléthyl)amino]éthyl]-acétanilide, le (R)-4'-[2-[(2-hydroxy-2-phényléthyl)amino]éthyl]-2-(2-pyridyl)acétanilide, le (R)-4'-[2-[(2-hydroxy-2-phényléthyl)amino]éthyl]-2-(2-pyrazinyl)acétanilide, le (R)-4'-[2-[(2-hydroxy-2-phényléthyl)amino]éthyl]-2-(2-pyrimidinyl)acétanilide, et des sels de ceux-ci.

5. Composition pharmaceutique contenant un composé selon l'une quelconque des revendications précédentes.

6. Utilisation d'un composé selon l'une quelconque des revendications 1 à 4 dans la préparation d'un médicament pour traiter le diabète sucré.